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THE DIAGNOSTIC VALUE OF DISALIGNMENT OF THE FOETAL CRANIAL VAULT BONES IN INTRA-UTERINE FOETAL DEATH

A roentgenologic study

by

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Overriding of the foetal cranial bones has occasionally been observed in intra-uterine foetal death, the change being due to shrinkage of the cerebrum (Fig. 1 a). This roentgenographic appearance, termed Spalding's sign, has been considered to be pathognomonic of intra-uterine foetal death (HORNER 1922, SPALDING 1922, VAN EBBENHORST TENGBERGEN 1926, JUNGMANN 1928, HENROTAY 1931, KEHRER 1931, SCHUMACHER 1933, HARTLEY 1939, NEUWEILER 1949, and others).

Overriding cannot take place unless it is preceded by disalignment of the bones concerned (Fig. 1 b). Disalignment of the foetal cranial bones has also been observed in intra-uterine foetal death and enables

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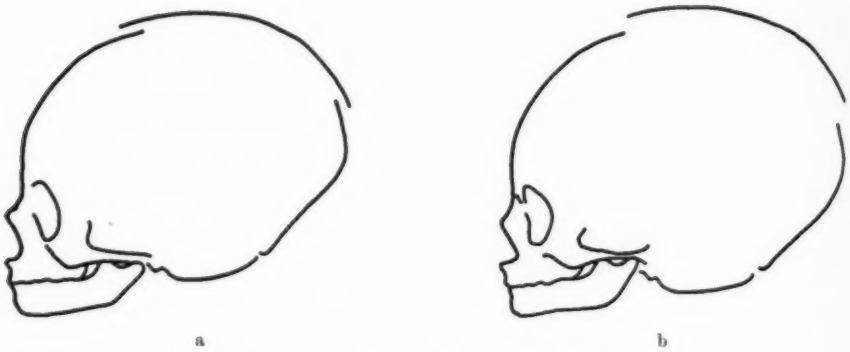

a b

Fig. 1. a) Foetal skull showing Spalding's sign. b) Disalignment.

the diagnosis to be made before Spalding's sign becomes positive (BRAKEMANN 1932, SCHUMACHER 1933, and others).

However, the condition has also been encountered in the living foetus and is then brought about by uterine contractions during labour. According to SCHUMACHER (1933) it may in rare exceptions also be observed prior to the onset of labour.

The present investigation was undertaken to determine whether there is a difference between the living and the dead foetus in respect to the degree of disalignment and the factors concerned.

It has been found that it is primarily the bones at the coronal and lambdoid sutures which show disalignment in conjunction with moulding of the foetal head, the change being due to inward or outward displacement of the parietal bone in relation to the frontal and occipital bones, respectively. For this reason the roentgenographic appearances of only these bones are discussed in greater detail.

Material and Methods

The roentgenograms obtained in 1,011 pregnant women were reviewed. In 969 cases the foetus was alive, presenting by the vertex in 891, and by the breech in 78. In 42 cases intra-uterine foetal death had occurred: in 32 of these the foetus presented by the vertex and in the remainder by the breech.

With the exception of some cases in which roentgenologic pelvimetry had been carried out, survey films of the abdomen had generally been taken. The focus—film distance was 90 or 100 cm. Only those roentgeno-

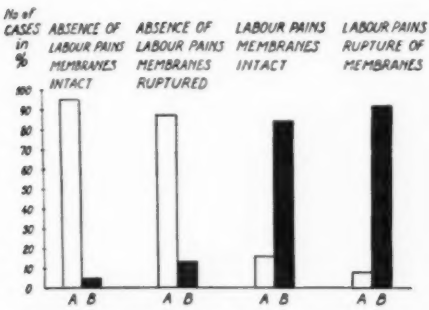

Diagram 1. Comparison of the number of foetuses showing disalignment (B) with the number in which it was absent (A) in living foetuses presenting by the vertex.

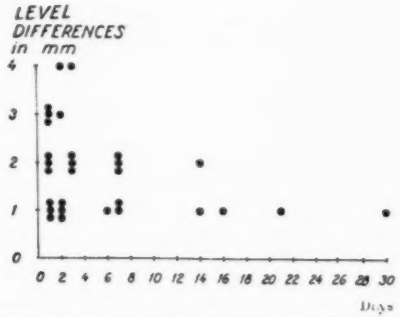

Diagram 2. Comparison between the degree of disalignment in living foetuses and the interval between roentgenologic examination and labour. Absence of labour pains. Membranes intact. 10th lunar month of pregnancy.

grams were included in which the foetal cranium and the areas around the coronal and lambdoid sutures were clearly visible. Level differences between the parietal and occipital and parietal and frontal bones were measured directly from the films and expressed in millimeters. Identical measurements were also carried out where overriding of the bones at these sutures was shown.

Findings

Roentgenologic appearances in the living foetus

Vertex presentation. Diagram 1 shows the findings in vertex presentations. This diagram was constructed from the roentgenologic appearances in 891 cases. These were divided according to the clinical findings at the time of the roentgen examination into the following four groups:

Group I Absence of labour pains, membranes intact (630 cases)
Group II » » » » » ruptured (60 cases)
Group III Labour pains, membranes intact (95 cases)
Group IV » » » ruptured (106 cases)

The distribution according to the month of pregnancy in which the roentgenologic studies were made was practically identical in the individual groups, the greater majority of the patients being in the ninth or tenth and the remainder in the seventh or eighth lunar month of pregnancy.

It is seen from Diagram 1 that 95 per cent of the foetuses in Group I did not show disalignment of the bones at the sutures in question. These findings suggest that it occurs rarely in the absence of labour pains and before rupture of the membranes. In the remaining 5 per cent (29 cases) the patient was in the tenth lunar month of pregnancy at the time of the roentgenologic studies. Diagram 2 shows that the great majority of the latter patients had been examined a few days before the onset of labour. The level differences varied between 1 and 4 mm, the greatest degree of disalignment being observed in the cases in which the patient had been examined shortly before labour. Painless uterine contractions appear to account for disalignment of the foetal cranial vault bones in this group.

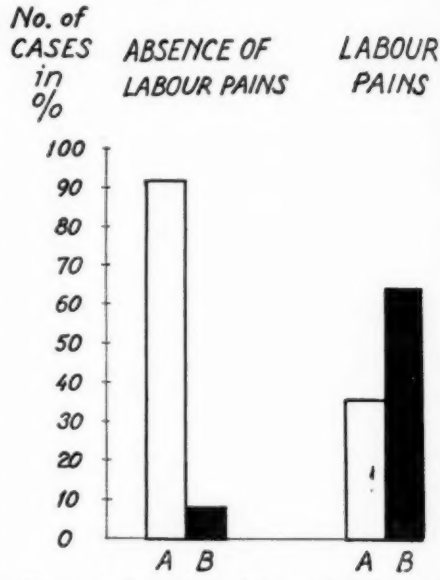

Diagram 3. Comparison of the number of cases in which disalignment (B) was observed with the number in which it was absent (A). Living foetuses presenting by the breech.

Of the 60 cases in Group II disalignment was observed in 8 only. These latter patients had been examined in the tenth lunar month of pregnancy; in no case did the level differences exceed 3 mm. There is apparently no relationship between rupture of the membranes and disalignment of the foetal cranial vault bones.

With the onset of labour disalignment was generally observed except in a few cases where it could not be identified. Marked disalignment was found in all cases in which the patient had intense labour pains and the foetal head was on the pelvic floor, the level differences between the parietal and occipital bones or frontal being as much as 10 mm in some cases (Groups III and IV).

The findings in these four groups suggest that disalignment of the foetal cranial vault bones observed prior to the tenth lunar month of pregnancy and in the absence of labour pains is a sign of foetal death. This also applies to level differences exceeding 4 mm identified in roentgenograms taken in the tenth lunar month of pregnancy in these cases.

Breech presentation. Diagram 3 shows the findings in breech presentation. Disalignment was rarely observed in the absence of labour pains.

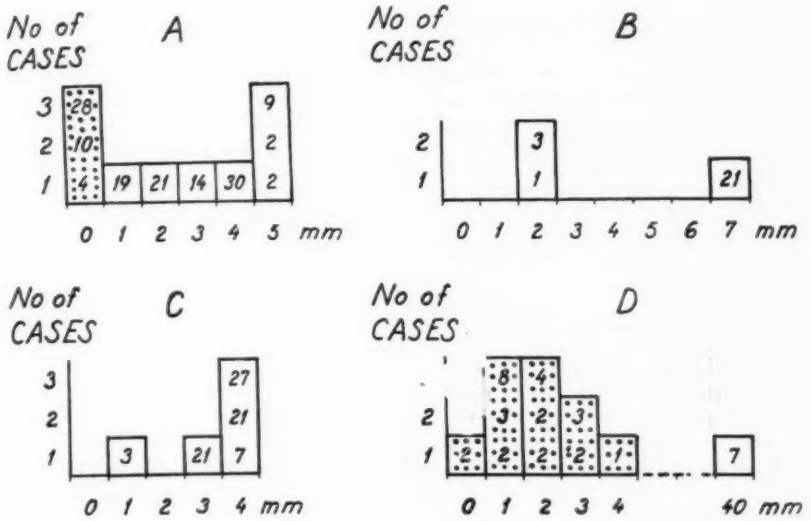

Diagram 4. Disalignment in dead foetuses and in absence of labour pains. Figures within individual blocks indicate the number of days the individual foetus had been dead. Blank blocks indicate cases in which foetal death was diagnosed from disalignment. Dotted blocks indicate cases in which diagnosis was not possible.

A — examined in 7th lunar month
B — » » 8th » »
C — » » 9th » »
D — » » 10th » »

Where it was found, the patient was in the tenth lunar month of pregnancy at the time of roentgenologic examination and the level differences did not exceed 4 mm. The findings in this group were practically identical with those in vertex presentation in the absence of labour pains.

As in vertex presentation marked disalignment was found in the presence of labour pains. However, in contrast to vertex presentation, where the parietal bone was found to be displaced outwards in relation to the occipital and frontal bones respectively, it was seen to be displaced inwards in one half of these latter cases.

Roentgenologic appearances in the dead foetus

Of the 42 cases in which intra-uterine foetal death had occurred, labour pains were absent and the membranes were intact in 29 at the time of the roentgenologic examination. Of these latter cases disalignment was observed in as many as 25. It is interesting to note that of

690 cases in which the foetus was alive and labour pains were absent, it was found in 37 only. These findings suggest that disalignment of the foetal cranial vault bones frequently occurs in intra-uterine foetal death, whilst it is rare in the living foetus.

Where labour pains were absent and the foetus was alive, level differences were observed only in the tenth lunar month of pregnancy and did not exceed 4 mm. It was therefore assumed that level differences observed before the tenth lunar month or level differences found in the tenth lunar month of pregnancy which exceed 4 mm, strongly suggest foetal death. This assumption prompted the investigation: (1) of the month of pregnancy in which foetal death had occurred, and (2) of the degree of disalignment in the 29 cases of intra-uterine foetal death.

Information about the date of foetal death was obtained from the hospital records of these patients. Diagram 4 shows that the criteria just discussed enabled the correct diagnosis to be made in as many as 16 cases.

In the remaining 13 of the 42 cases in this group the foetus was dead and intense labour pains were present. Disalignment, which often was quite marked, was found in several of these cases. However, in the presence of labour pains it is not suggestive of foetal death because it may also be observed in cases of a living foetus during labour.

SUMMARY

The value of disalignment of the foetal bones at the coronal and lambdoid sutures in the diagnosis of intra-uterine foetal death has been investigated. Disalignment of these bones observed prior to the tenth lunar month of pregnancy and in the absence of labour pains strongly suggests death of the foetus. Level differences between these bones exceeding 4 mm, observed in the tenth lunar month of pregnancy and in the absence of labour pains, are likewise suggestive of foetal death but not disalignment of these bones observed during labour. Of 29 cases of intra-uterine foetal death, where labour pains were absent, these criteria enabled the correct diagnosis to be made in 16.

ZUSAMMENFASSUNG

Der Wert einer Niveauverschiebung der foetalen Knochen an der Sutura coronalis und der Sutura lambdoidea für die Diagnose des intrauterinen Foetustodes ist untersucht worden. Derartige Lageveränderungen dieser Knochen, die vor dem 10. Schwangerschaftsmonat bei Abwesenheit von Wehen beobachtet worden sind, sprechen für den Tod des Foetus. Niveauunterschiede zwischen diesen Knochen von mehr als 4 mm, welche im 10. Schwangerschaftsmonat ohne Wehen beobachtet werden, sprechen ebenfalls für einen Foetustod; nicht dagegen Niveauunterschiede dieser Knochen, die während der Wehen beobachtet wurden. Bei 29 Fällen mit intrauterinem Foetustod, bei denen Wehen fehlten, erlaubten diese Kriterien die Stellung einer korrekten Diagnose in 16 Fällen.

RÉSUMÉ

Les auteurs ont étudié la valeur du chevauchement des os foetaux au niveau des sutures coronale et lambdoïde pour le diagnostic de la mort foetale intra-utérine. Le chevauchement de ces os constaté avant le dixième mois lunaire de la grossesse et en l'absence de douleurs du travail rend très probable la mort foetale. Les différences de niveau entre ces os dépassant 4 mm et constatées au cours du dixième mois lunaire de la grossesse, en l'absence de douleurs du travail, doivent aussi faire penser à la mort foetale, mais non le chevauchement de ces os constaté au cours du travail. Sur 29 cas de mort foetale intra-utérine sans douleurs du travail, ces critères ont permis de porter le diagnostic exact dans 16 cas.

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CALCIFICATION IN CARCINOMA OF THE STOMACH

by

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Roentgenologic signs of calcifications in tumours are by no means uncommon. This applies to malignant as well as to benign tumours and to epithelial as well as mesenchymal growths.

The frequency of calcifications varies, however, according to the nature of the tumour; thus they are commonly found in uterine fibromyomas, and abnormal intracranial calcareous deposits may be an important diagnostic feature in brain tumour. On the other hand, calcifications appear to be rare in tumours affecting the alimentary tract, although they may be observed, *e. g.* in argentaffine carcinoids of the appendix. Roentgenologic signs of calcification in gastric tumours seem to be exceedingly uncommon and only 9 cases have been reported, the last by KENDIG et coll. (1957). BATLAN (1954) gave a detailed review of the literature to which the author is now able to add a further case.

Case report

A farmer, aged 77, who twenty years previously had been admitted to another hospital with haematemesis apparently caused by duodenal ulceration. His symptoms disappeared following treatment. During the previous 3 or 4 months increasing fatigue and dyspnoea on exertion, but no loss of weight. Haemoglobin 73 %. E. S. R. 70 mm/hour. Occult blood: Highly positive reaction 6 times. W. R.: Negative.

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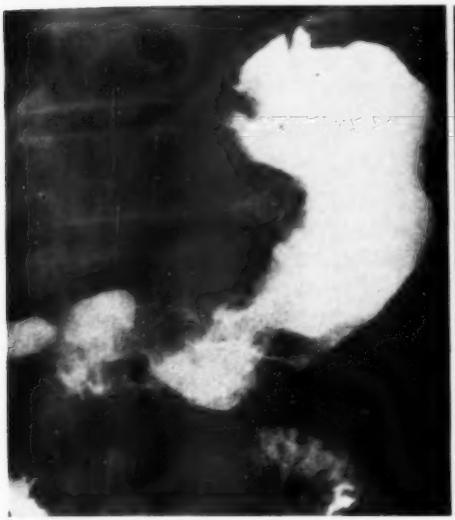

Fig. 1. Extensive tumour infiltration in the ventricle, extending from the cardia to the pylorus. Calcareous deposits.

Fig. 2. Gas-filling of the ventricle. In the fornix the wall is unchanged. In the corpus and canalis egestorius the walls are considerably thickened. Numerous small calcium deposits in the walls.

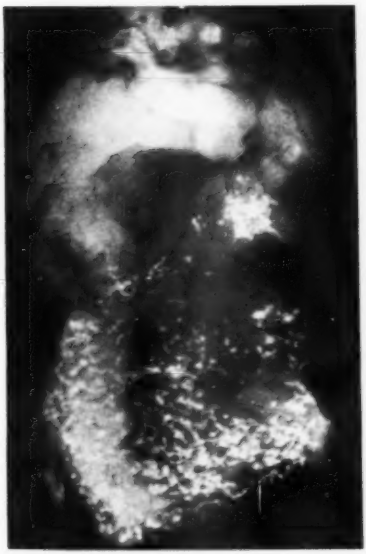

Fig. 3. Roentgenogram of operative specimen. Area of fornix without calcification. Lower down, in the wall, numerous granular calcifications.

Roentgenography of the stomach (Fig. 1) revealed a diffuse lesion with irregular dentate outlines, extending from the prepylorus almost up to the cardia. On fluoroscopy the gastric wall appeared to be firm and unyielding and the diagnosis of a tumour seemed to be beyond doubt. Calcifications of unusual appearance were noted in the superoposterior region of the abdomen, and the films which were obtained before and after the administration of contrast media seemed to indicate that the calcifications were situated in a greatly thickened gastric wall (Fig. 2). An explanation of their presence was not, however, obvious.

The diagnosis of a growth was confirmed at operation. A roentgenogram of the specimen is shown in Fig. 3. The gastric mucosa was greatly thickened, irregular, and ulcerated from a few centimetres below the cardia to about 4 cm from the pylorus. In several regions the gastric wall was up to 2 cm thick; on section the tissue was whitish and partially transparent; especially superiorly it contained numerous small granules of calcifications.

Microscopy revealed infiltrating tumour tissue consisting of large islets of tumour cells with typically polymorphous and hyperchromatic nuclei. The picture was predominated by colloid which displaced the nuclei towards the periphery, and within which there were here and there irregular depositions of calcium.

Discussion

A common feature of all the published cases of gastric carcinoma with roentgen signs of calcification has been that the tumours have been mucinous adenocarcinomas. This is probably not mere chance. It is generally recognized that devitalized or dead tissue which is surrounded by living tissue has a tendency to calcify. This applies to *e. g.* caseous tuberculous lesions, old empyemas, and necrotic renal tubules following corrosive sublimate poisoning. The encased tissue is transformed into a hyaline material which biochemically is closely related to the mucinous substance found in mucoid carcinomas. In such areas the carbon dioxide tension is low and this is no doubt a factor in the unelucidated chemical processes which lead to the deposition of calcium.

Calcifications in gastric carcinomas do not appear to increase with advancing age. TENCONI (1948) has reported the phenomenon in a 27-year-old man and the average age of the cases published so far was 42 years.

SUMMARY

Roentgenographic signs of calcifications were found in carcinoma of the stomach in a 77-year-old man. The tumour was a mucinous adenocarcinoma.

ZUSAMMENFASSUNG

Röntgenologisch sind Verkalkungen in einem Cancer ventriculi eines 77-jährigen Mannes gefunden worden. Histologisch war der Tumor ein schleimbildendes Adenocarcinom.

RÉSUMÉ

L'auteur a trouvé des signes radiographiques de calcifications dans un cancer de l'estomac chez un homme de 77 ans. Histologiquement cette tumeur était un adénocarcinome mucoïde.

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SKELETAL LESIONS IN LEUKAEMIA IN CHILDREN

by

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Skeletal lesions in leukaemia were first demonstrated roentgenographically by VON JAKSCH in 1901, and during the subsequent decades a number of single cases were reported. In the thirties and forties, series of children with leukaemic bone changes were published, the largest by SILVERMAN in 1948 with an excellent review of the literature. From Scandinavia, BRANDBERG in 1942 reported 3 cases, but no comprehensive series has been published to date.

Interest in these conditions has now been revived by reason of the prolongation of the survival time of leukaemic patients by antileukaemic drugs (such as ACTH and cortisone-like agents, aminopterin and the like, and 6-mercaptopurin). The findings in 32 children admitted to our departments are now presented.

Leukaemic lesions of the bones may be divided into four roentgenologic types with the following predominant characteristics: 1) Translucent zones in the metaphyses, 2) destructive changes, 3) subperiosteal new bone formation, and 4) osteosclerosis.

Metaphyseal changes (Fig. 1). These changes manifest themselves as transverse bands of diminished density, 1 to 7 mm wide, in the metaphyses of the long bones. As a rule, they are bilateral, and usually affect the

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Fig. 1. Boy, aged 5 years. Transverse bands of decreased density. Similar findings were present in other long bones.

Fig. 2. Girl, aged 3 years. Focal osteoporosis. Transverse bands of decreased density also present.

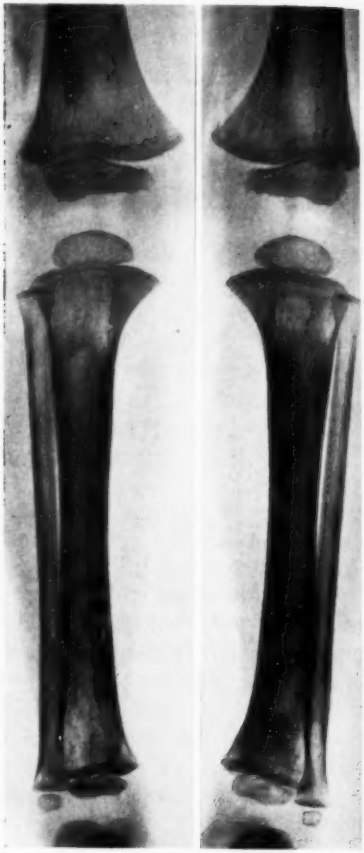

Fig. 2

distal part of the femur and the proximal part of the tibia or the distal ends of the radius and ulna. Metaphyseal translucencies are generally the first roentgenographic signs of skeletal lesions. They have been seen as early as 4 weeks after the first clinical signs of acute leukaemia. These changes are not, however, specific of leukaemia. Similar appearances have been reported after immobilization (GRIFFITHS), in bacteriaemia, primary tuberculosis with haematogenous spread, scurvy, metastatic neuroblastoma (SILVERMAN), congenital syphilis, atresia of the biliary tract, cystic fibrosis of the pancreas, and malnutrition, as well as in a few healthy newborn infants (DALE). They are caused by focal skeletal

destruction by proliferating leukaemic tissue, and their situation is believed to be due to local factors, such as the blood supply to these sites. Spontaneous disappearance of the changes has been observed in exceptional cases (SILVERMAN, DALE).

Destructive changes (Fig. 2). These appear in the roentgenogram partly as focal translucencies in the spongiosa and cortex, including the epiphyses, and partly as diffuse osteoporosis involving the entire bone. There is no sharp distinction between the focal lesions and metaphyseal changes. The destructive changes may be encountered in all bones, but particularly in the pelvis and vertebral bodies, in which latter situation they may give rise to collapse and spontaneous fractures. The lesions are due to infiltration by the leukaemic tissue and erosion of the bone.

Fig. 3. Boy, aged 5 years. Subperiosteal new bone formation. Similar changes and focal osteoporosis in other bones were found.

Fig. 4. Boy, aged 2 years. Diffuse osteoporosis and increased intervertebral spaces.

Fig. 4

Subperiosteal new bone formation (Fig. 3). This type is manifest in the roentgen film as linear densities parallel to and separated from the bone, spreading segmentally or along the entire length of the shaft, the cortex presenting a double outline. In rare cases, radiating spicules may be evident (GRIFFITHS). The explanation of these changes is presumably that the proliferating leukaemic tissue elevates the periosteum, the osteoblasts of which form a new layer of bony tissue around the original bone.

Table 1

Frequency of roentgen changes in 4 different series

	Total	Roentgen changes	Metaphyseal	Destructive	Periosteal	Osteosclerosis
Baty & Vogt (1935) Infants' and Children's Hosp. and Dep. Pediatr. Harvard Med. School, Boston	43	30	30	2	2	0
Dale, Jr. (1949) Children's Clinic of the New York Hospital	40	29	27	12	7	0
Landolt (1946) Kinderspital, Zürich	37	29	22	21	4	1
Silverman (1948) Babies Hospital, New York...	103	52	14	39	17	9
Total	223	140	93	74	30	10

Osteosclerosis. These changes may be diffuse in one bone or generalized. Their pathogenesis is in doubt.

The reported frequency of bone lesions in children with leukaemia varies between 50 and 75 per cent. Out of 223 children in the four largest series published to date 140 exhibited roentgenographic changes, most often metaphyseal translucencies and only rarely osteosclerosis (Table 1).

Present investigation

Material. During the period 1946 to July 1957 a total of 47 children with leukaemia were admitted to our hospital. Out of this number, 32 were selected at random and underwent roentgenographic examination of the entire skeletal system, once or more, in an attempt to demonstrate leukaemic lesions.

Age distribution. The patients, 17 boys and 15 girls, ranged in age from 8 months to 13 years at the onset of the disease, that is from the time at which the first definite symptoms of leukaemia were reported to have appeared. Nineteen of the 32 patients were under 7 years of age.

Type of leukaemia. All the patients were suffering from acute 'stem-cell' leukaemia. No distinction will be made between myeloblastic and lymphoblastic leukaemia.

Occurrence of skeletal lesions. Twenty patients (10 boys and 10 girls) had roentgen signs of leukaemic skeletal lesions. The skeletal lesions were most common in the lower age groups, with no case in the 11 to 14 age range.

Translucent zones of the metaphyses were observed in 18 cases and was the only finding in 12; in 2 cases they were not prominent. Destructive changes were seen in 8 cases in the form of patchy osteoporosis in 5 and diffuse osteoporosis in 3. One of the children had advanced vertebral changes with marked diffuse osteoporosis, 'fish vertebrae', and rather wide intervertebral spaces. (Fig. 4). Periosteal changes were present in 5 cases and osteosclerosis in 1.

Time of roentgenography. Out of the 32 patients, 20 were examined within 4 months after the onset of symptoms, and 8 showed bone changes. In at least one of these the changes were present a month after the commencement of the disease. Eight patients were examined for the first time 4 to 6 months after the onset, and 6 showed abnormalities. The remaining 4 patients did not have roentgen investigations until their disease was of more than 6 months' standing, and 2 showed bone lesions. Eight of the patients, 7 of whom had bone lesions, were receiving specific treatment when the first roentgen examination was made; at that time, however, none of the patients were in complete haematologic remission. Further roentgenography, three months or so later, of 8 patients who had previously shown normal roentgen appearances revealed skeletal lesions in 4; in another, however, there were still no changes 10 months later.

Bone pain. Thirteen patients (7 boys and 6 girls) had bone pain and/or tenderness. In 12 of them roentgenography showed skeletal lesions.

Relation to treatment. Repeated roentgenography during treatment with antileukaemic drugs was made in 15 patients. Out of 8 patients with bone changes prior to treatment, 2 exhibited entirely unchanged roentgen changes after treatment for one month and remission, whereas in 2 patients with remission the changes increased during the following year. In 3 patients the roentgen changes had decreased after 4 to 6 months of treatment, and, lastly, in one patient with remission the changes disappeared completely for one month but reappeared as a relapse occurred.

Out of 7 patients without bone changes prior to treatment, 3 had developed skeletal changes after treatment for 3 to 11 months.

SUMMARY

In a material of 32 children with acute leukaemia 20 had skeletal roentgenologic changes. Transverse bands of diminished density in the metaphyses were demonstrated in 18 patients, patchy osteoporosis in 5 and diffuse osteoporosis in 3, subperiosteal new bone formation was observed in 5 and osteosclerosis in one patient. Nearly half the number of patients had bone pain and all but one of these had skeletal changes. The lesions were often present within the first 4 months after the onset of clinical manifestations. The effect of treatment with antileukaemic drugs upon the bone changes varies.

ZUSAMMENFASSUNG

Von 32 Kindern mit akuter Leukämie hatten 20 röntgenologische Skelettveränderungen. Metaphysäre Querstreifen mit herabgesetzter Dichte wurden bei 18 Patienten demonstriert, fleckige Osteoporose bei 5 und diffuse Osteoporose bei 3 Patienten, subperiostale Knochenneubildung bei 5 Patienten und Osteosklerose bei einem Patienten. Nahezu die Hälfte der Patienten hatten Knochenschmerzen und mit einer Ausnahme hatten alle Skelettveränderungen. Die Knochenschädigungen sieht man oft innerhalb der ersten 4 Monate nach dem Auftreten der klinischen Manifestationen. Die Wirksamkeit der Behandlung mit antileukämischen Drogen variiert.

RÉSUMÉ

Sur une série de 32 enfants atteints de leucémie aigüe, 20 avaient des signes radiographiques de lésions osseuses; on a mis en évidence chez 18 de ces malades des bandes transversales d'opacité diminuée dans les métaphyses, une ostéoporose en taches chez 5 malades, une ostéoporose diffuse chez 3, une néoformation sous-périostée d'os chez 5 malades et une ostéosclérose chez un malade. Près de la moitié des malades avaient des douleurs osseuses, et parmi ceux-ci, tous sauf un présentaient des lésions du squelette. Les lésions osseuses existent souvent dans les 4 premiers mois après le début clinique de la maladie. L'effet du traitement par les médications antileucémiques est variable.

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BLOOD CIRCULATION DURING AND AFTER PERIPHERAL ARTERIOGRAPHY

Experimental study of the effects of Triurol (sodium acetrizoate) and Hypaque (sodium diatrizoate)

by

Percy Lindgren and *Gunnar Törnell*

The majority of water-soluble iodine compounds which have come into use for intravenous or intra-arterial administration are reported to produce various effects upon the circulation. In studying these effects, most workers have drawn their conclusions solely from blood-pressure recording. The commonest reaction in angiography and aortography, etc, as well as in intravenous injection has been a fall of blood pressure.

ROBB and STEINBERG (1939), for instance, observed a blood-pressure fall of around 30 mm Hg, and an increase of about 30 beats per minute in the heart rate, 10 to 20 seconds after the rapid intravenous injection of 25 to 45 ml Diodrast. They attributed these reactions to a direct vasodilator effect. Numerous authors have reported similar hypotensive actions

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of different contrast media in both laboratory animals and human subjects (WEATHERALL 1942, HOWARTH 1950, GORDON et coll. 1950, ROWE et coll. 1956, ZSEBÖK et coll. 1954, COTRIM 1954, and AMUNDSEN et coll. 1956, among others).

There is some diversity of opinion as regards the direct effect of iodine contrast media on the peripheral blood vessels. The investigations in this field are, however, few in number and some of them have been conducted with unsatisfactory techniques. KRAUS (1935), in animal experiments with a technique that was good for those days, observed a vasodilator action of the contrast media Abrodil, Perabrodil and Uroselectan. He reported, for example, that 1 ml Abrodil 40 % injected intra-arterially into the leg of a dog had a vasodilator effect equivalent to 0.1 μg acetylcholine. In perfused rabbit ear and dog's leg (defibrinated blood; Dale-Schuster pump), WEATHERALL (1942) observed slight vasodilatation, sometimes preceded by slight initial vasoconstriction, after intra-arterial injections of Diodone and Iodoxyl. FOLTZ, THOMAS and WARD (1952), in direct observations of pial vessels via a Forbes window in monkeys and cats, found marked angiospasm and cortical pallidity on carotid angiography with Diodrast. Cerebral vasoconstriction following intracarotid injections of Umbradil was recently reported by INGVAR and SÖDERBERG (1957), who used a direct method for measuring the blood flow in the brains of cats. The vasoconstrictor effect of Diodrast was disputed, however, by BROWNE and STERN (1954) and SCHMIDT (1955), who on the other hand, found dilatation of the pial vessels.

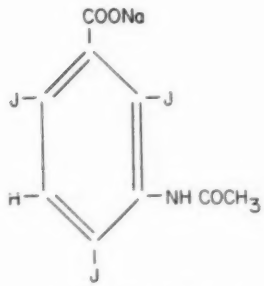
In the last few years tri-iodo-benzoic acid derivatives have been widely used as contrast media. The aim of the present experimental investigation was to study the effect of two of these agents on the peripheral blood vessels in arteriography.

Method

The experiments were performed on 19 cats weighing 2.0 to 3.7 kg, anesthetized with Dial (40 to 70 mg/kg, injected intravenously).

The *arterial blood pressure* was recorded in the brachial or femoral artery, which was cannulated and connected to an ordinary mercury manometer.

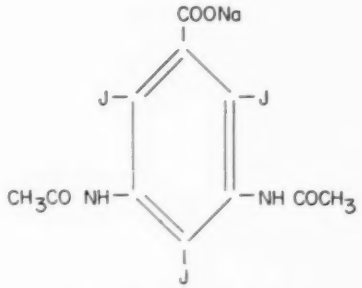
The *blood flow* in different vascular areas was recorded by a technique described in detail by LINDGREN and UVNÄS (1954) and LINDGREN (1955). In principle the method consisted in directing the blood flow from a cannulated vein, via a plastic tube, to a drop chamber. A phototube drop counter operated an ordinate recorder and from the drop chamber the blood stream was returned to the animal, entering the cannulated proximal stump of the same vein. The records, directly proportionate to the drop intervals and



MOL WEIGHT 579, 66% IODINE
SODIUM 3-MONOACETYL-AMINO-2,4,6-TRIIODOBENZOATE

SODIUM ACETRIZOATE

ACÉTIODONE
DIAGINOL
RHEOPAK
TRIUROL
UROKON



MOL WEIGHT 636, 60% IODINE
SODIUM 3,5-DIACETYL-AMINO-2,4,6-TRIIODOBENZOATE

SODIUM DIATRIZOATE

HYPAQUE

indirectly proportionate to the rate of flow, were calibrated in milliliters per minute. In order to prevent clotting, heparin 25 mg/ kg in a 5 per cent solution was given intravenously.

The *muscle blood flow* was studied in a hind leg. In order to eliminate the blood flow from other types of tissues (notably the skin) the leg was skinned and a tight ligature was applied immediately above the ankle, which isolated the paw from the circulation; the detached skin was wrapped round the isolated muscles and sutured to obviate cooling. The cannula was inserted in the femoral vein.

The *cutaneous blood flow* from a paw was recorded in the great saphenous vein or the cephalic vein.

The *intestinal blood flow*, from a segment of the ileum, was recorded in an arcade vein. Contiguous arcade veins were ligated so as to block any collateral pathways. After insertion of the cannula the greater part of the abdominal incision was sutured.

Intra-arterial injections into a hind leg were given through a thin plastic tube inserted into the central stump of a ligated and cut side-branch of the femoral artery. The arrangement in the intestinal region was similar.

Chemistry of the contrast media employed. The formulae of sodium acetrizoate and diatrizoate are given above. We employed the marketed solutions, Triurol (Leo) and Hypaque (Winthrop) (supplied by AB Leo, Hälsingborg and AB Erco Pharmaceuticals, Stockholm). These preparations are stated to contain, in addition to the contrast agent, small amounts of calcium dipotassium and calcium disodium versenate, respectively.

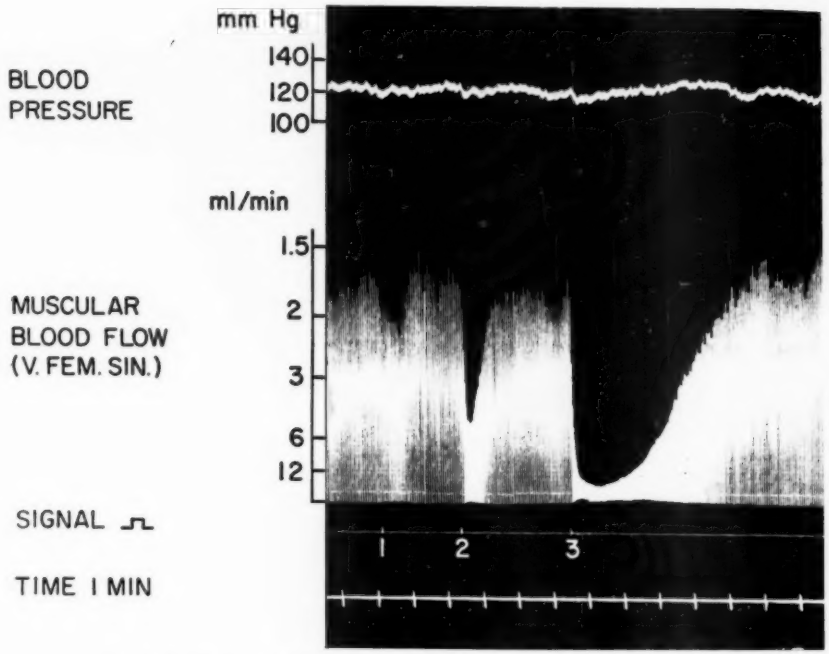


Fig. 1. Cat 2.1 kg. Dial 65 mg/kg. Comparison of effects on muscular blood flow of the following injections, in an amount of 0.05 ml:

	Increase of flow	Duration
1. 0.9 % NaCl (left femoral artery)	10 %	1 min
2. Hypaque 45 %	180 %	1 »
3. Triurol 50 %	800 %	5 »

as stabilizing substances. We used 25, 35, 50 and 70 per cent solutions in our study of Triurol and a 45 per cent solution in the case of Hypaque. Special roentgenologic interest attaches to the iodine content of these agents and this is tabulated below.

		Iodine mg/ml
Sodium acetrizoate (Triurol)	25%	165
	35%	231
	50%	330
	70%	462
Sodium diatrizoate (Hypaque)	45%	270

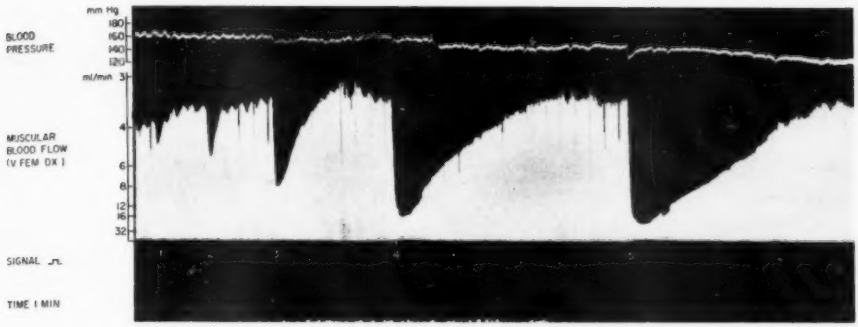


Fig. 2. Cat 3 kg. Dial 50 mg/kg. Vasodilator effects of intra-arterial injections of 0.1 ml NaCl and Triurol, the latter in increasing concentrations:

	Increase of flow	Duration
1. 0.9 % NaCl	20 %	0.5 min
2. Triurol 25 %	50 %	1 »
3. Triurol 35 %	130 %	3 »
4. Triurol 50 %	370 %	10 »
5. Triurol 70 %	550 %	13 »

Results

A constant observation in all experiments was the increase in the blood flow which followed the intra-arterial injection of both the preparations. The difference in the respective magnitudes of the increase was, however, substantial; sodium acetrizoate had a vasodilator action many times greater than that of sodium diatrizoate.

Skeletal muscle. Only the blood pressure and muscle blood flow were recorded in most experiments. The result of a typical experiment is shown in Fig. 1. By injecting 0.05 ml 0.9 per cent saline we first investigated the effect of the injection itself. This was of a mechanical and thermal nature and resulted in a brief minimal increase in the blood flow — an ordinary reaction. We then tested corresponding volumes of Hypaque 45 % and Triurol 50 % (Nos. 2 and 3 in the figure). (The injected solutions were of room temperature, about 23 °C, because experiments with slightly heated solutions had been found to give the same results.) The difference in effect was striking. While Hypaque produced very moderate vasodilatation of short duration, the blood flow rising from 1.8 to 5 ml per minute, Triurol caused virtually maximal vasodilatation — from 1.8 to about 16 ml per minute — the vasodilatation not disappearing until some 5 minutes had elapsed. There was no effect whatsoever on the blood pressure. The injection of Triurol, it is true, must have greatly reduced the peripheral

Table

Increase of muscular blood flow (femoral vein) after intra-arterial injections of contrast media in varying amounts and concentrations. Mean values from 19 experiments. The figures in parentheses are unreliable and based on only a few observations.

Amounts injected:	0.025 ml	0.05 ml	0.1 ml	0.2 ml
Na-acetrizoate 25 % ..... (Triurol)		(67 %, < 1 min)	110 %, < 1 min	240 %, 1.5 min
» 35 %		96 %, < 1 min	228 %, 2.8 min	(637 %, 5.0 min)
» 50 %	178 %, 2.6 min	521 %, 5.4 min	785 %, 8.0 min	999 %, 8.3 min
» 70 %		(759 %, 9.0 min)	886 %, 13.3 min	
Na-diatrizoate 45 % .... (Hypaque)		41 %, < 1 min	76 %, < 1 min	87 %, 1.3 min
NaCl 0.9 %		< 10 %, < 1 min	26 %, < 1 min	40 %, < 1 min

resistance, but this effect was localized solely to the left hind leg and could have brought about only a very slight change in the total peripheral resistance. The amount injected, moreover, was far too small to produce general effects when it entered the circulation.

Significance of the concentration of the solution. To elucidate the significance, if any, of the solution's concentration for the major increase in blood flow, we studied concentrations of Triurol varying from 25 to 70 per cent. Fig. 2 shows the result of one of these experiments (Cf. the Table and the Diagram below). It was mainly the higher concentrations, of 50 and 70 per cent, that had a powerful vasodilator effect. What is striking in this case is not only the great increase, at its maximum, but also the long duration; there was an interval of 10 to 12 minutes before the blood flow in the relevant area had returned to normal.

Another interesting observation is that the higher concentrations had a disproportionately greater effect than the lower ones, *i. e.* the decisive factor probably was not the amount of the substance injected but rather its concentration. A corollary is that 0.05 ml of Triurol 50 % has a greater effect than 0.1 ml of 25 %. This fact is clearly evident from the table and the dose response curves in the diagram. The vasodilatation produced by the higher concentrations may be regarded as practically maximal in doses exceeding 0.1 ml. A further increase of the dose resulted chiefly in a prolongation of the time required for the blood to return to normal.

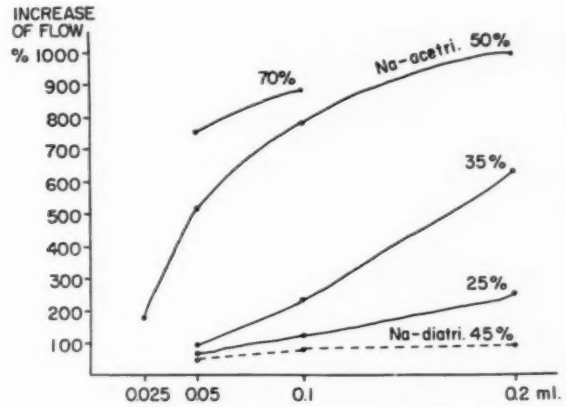


Diagram. Dose-response curves in accordance with the mean values in the table on opposite page.

The difference between the effects of Triurol and Hypaque seems quite obvious and it is not likely to be due to any difference in the osmotic behaviour or in viscosity. Hypaque 45 % in the osmotic sense lies between Triurol 35 % and Triurol 50 %, yet its vasodilator effect is lower than that of Triurol 25 %.

Mode of action of the contrast media. The increase of blood flow produced in skeletal muscle by Triurol is equally great as that, for example, of large amounts of acetylcholine injected intra-arterially, but its duration is far greater. We are therefore probably concerned here with a virtually total paralysis of the smooth muscle of the arterioles. The degree of this vascular paralysis is evident from the experiment shown in Fig. 3. During vasodilatation produced by Triurol the vessels were quite unresponsive to a powerful vasoconstrictor —noradrenaline. The dose (No. 1 in Fig. 3) of 1 μg noradrenaline injected into the femoral artery gave under normal conditions rise to marked vasoconstriction and a resulting decrease in the blood flow. In maximal vasodilatation following injection of Triurol, this dose of noradrenaline had not the slightest effect (No. 3 in Fig. 3). Nor was a tenfold greater dose (No. 4 in Fig. 3) able to induce any vasoconstriction; under normal conditions this dose had substantially increased the peripheral resistance in the vascular area, with virtually total stasis. Noradrenaline, as will be seen, had a powerful systemic effect when it entered the circulation, which fact indicates the strength of the dose.

It was not our aim to study in detail the mechanism of the vascular paralysis caused by Triurol; but it is worthwhile mentioning that we were

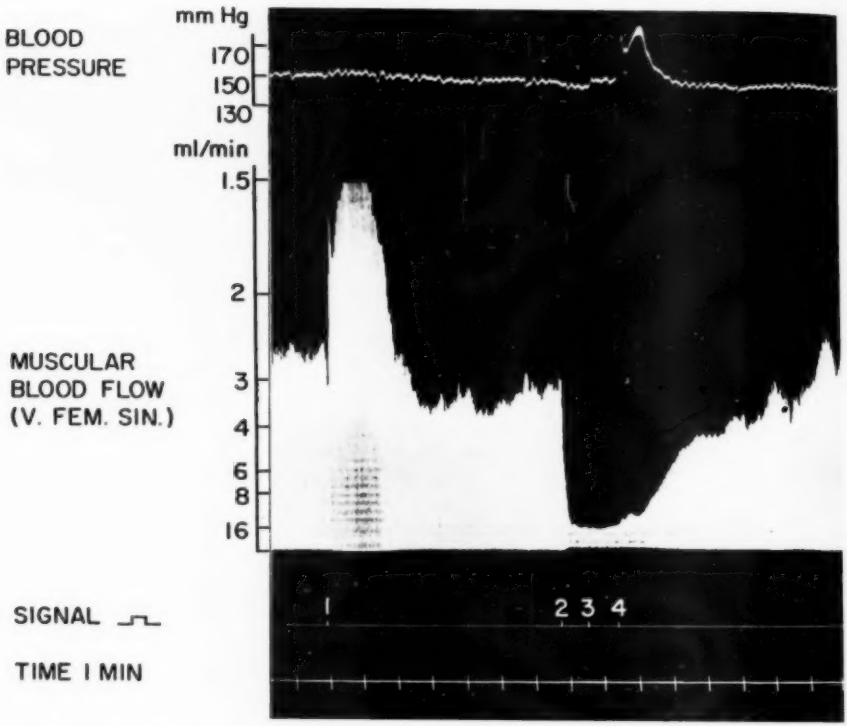


Fig. 3. Cat 2.1 kg. Dial 50 mg/kg. Influence of noradrenaline on muscle vessels under normal conditions (1) and during Triurol vasodilatation (3 and 4). Noradrenaline was quite inactive in the latter case.

1. 1 μg 0.1 ml noradrenaline I. A.
2. 0.1 ml Triurol I. A.
3. 1 μg 0.1 ml noradrenaline I. A.
4. 10 μg 0.1 ml noradrenaline I. A.

unable to block the vasodilatation with antihistaminics or by atropinization (Fig. 4).

Intestine. The vascular characteristics of the splanchnic region and skin diverge in several respects from those of skeletal muscle. For instance, the vasomotor innervation differs: skeletal muscle vessels have both constrictor and dilator nerves, the cutaneous and intestinal vessels only constrictor nerves.

The reaction of intestinal vessels to arteriography with Triurol and Hypaque was similar to that in the case of skeletal muscle. Hypaque produced only a slight transient increase of flow in that part of the ileum

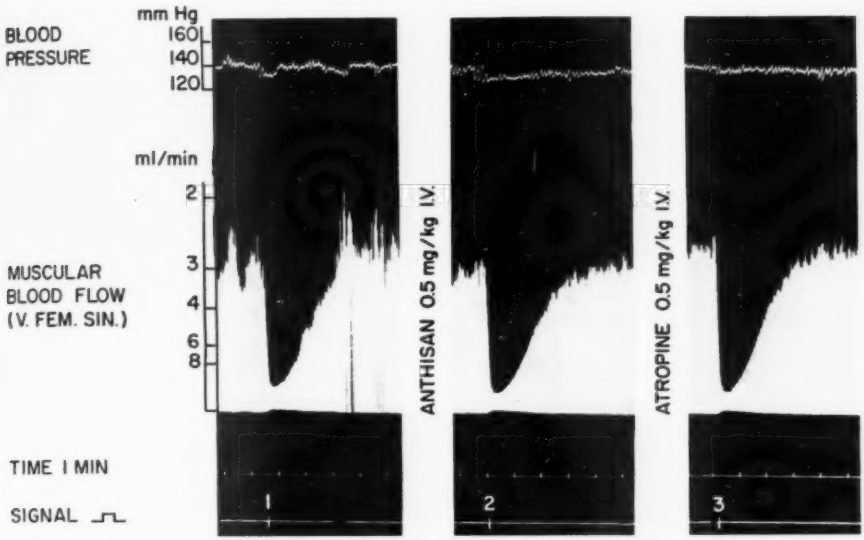


Fig. 4. Cat 2.4 kg. Dial 40 mg kg. Triurol vasodilatation is uninfluenced by antihistaminic and anticholinergic drugs.

1, 2 and 3: Injection of 0.05 ml Triurol 50 % into the left femoral artery.

Between 1 and 2: Anthisan 0.5 mg/kg I. V. Between 2 and 3: Atropine 0.5 mg/kg I. V.

from which the recording was made (Fig 5). Triurol, on the other hand, caused marked and prolonged vasodilatation of the same character as that in the muscles.

Skin. On recording of the venous outflow from a cutaneous area, a front or hind paw — the injection being given into the brachial or femoral artery similarly to that for measurement of the blood flow in hind leg muscles, *i. e.* in the proximal part of the artery — it was found that the blood flow was substantially reduced after the injection of Triurol whereas Hypaque caused no major change.

An experiment of this type is illustrated in Fig. 6. Since Triurol is unlikely to have a different effect on cutaneous than on muscle and intestinal blood vessels, we imagined that purely hemodynamic factors were involved. With the injection of the contrast medium into the proximal part of the brachial artery, extreme vasodilatation occurs in the skeletal muscles of both the upper arm and forearm and, probably, other tissues in those regions. As a result the blood pressure in the more distal

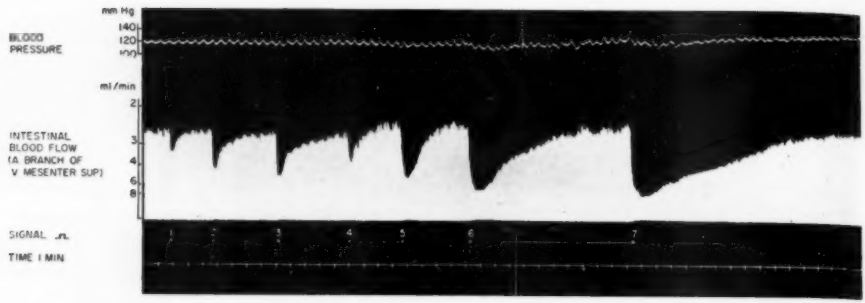


Fig. 5. Cat 2.2 kg. Dial 65 mg/kg. Vasodilator effects of various doses of Hypaque and Triurol on intestinal blood flow:

				Increase of flow	Duration
1.	0.1	ml	Hypaque 45 %	25 %	1 min
2.	0.2	»	» 45 %	60 %	2 »
3.	0.4	»	» 45 %	80 %	4 »
4.	0.05	»	Triurol 50 %	40 %	1 »
5.	0.1	»	» 50 %	100 %	3 »
6.	0.2	»	» 50 %	180 %	7 »
7.	0.4	»	» 50 %	220 %	12 »

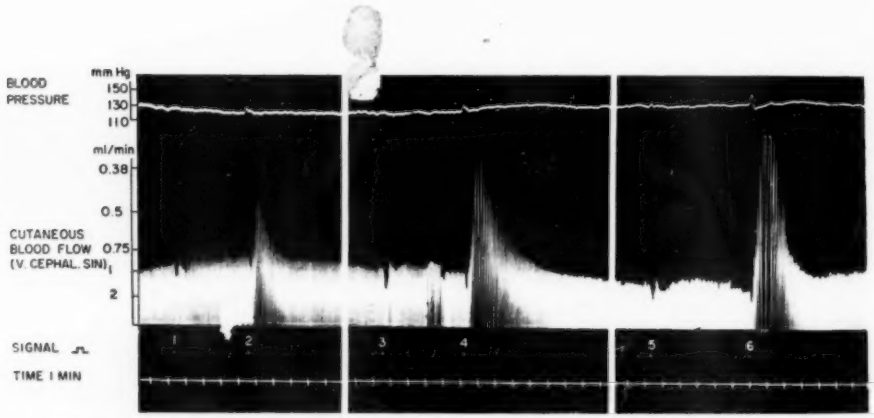


Fig. 6. Cat 2.5 kg. Dial 50 mg/kg. Changes in blood flow from a skin area (a forepaw) after injections of Hypaque and Triurol into a cannulated side branch of left brachial artery:

				Decrease of flow	Duration
1.	0.05	ml	Hypaque 45 %	—	—
2.	0.05	»	Triurol 50 %	40 %	2 min
3.	0.1	»	Hypaque 45 %	—	—
4.	0.1	»	Triurol 50 %	65 %	4 min
5.	0.2	»	Hypaque 45 %	—	—
6.	0.2	»	Triurol 50 %	80 %	4 min

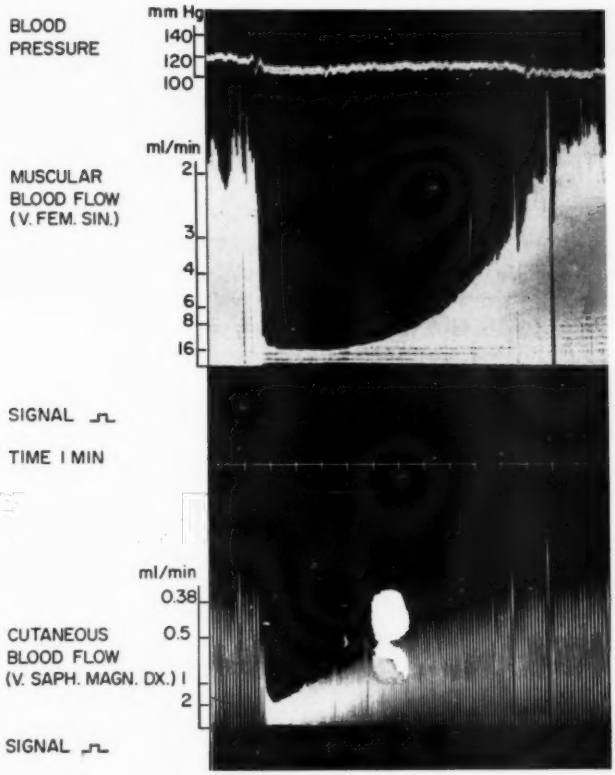


Fig. 7. Cat 2.0 kg. Dial 55 mg/kg. Vasodilator effects of Triurol on muscular and cutaneous blood flow. 0.5 ml Triurol 50 % injected into abdominal aorta (via the cannulated proximal stump of inferior mesenteric artery). Increase of muscular blood flow > 1,000 %, duration 12 min; cutaneous blood flow 400 %, 10 min.

parts of the arm arteries falls to such a degree that the flow is reduced in the most peripheral regions — from which the venous outflow in this case was recorded — even though vasodilatation probably exists there too.

That this explanation is correct and that Triurol even has a dilator effect on cutaneous vessels seems clear from the following experiment (Fig. 7). We here made the injection into the abdominal aorta and recorded both the muscle blood flow in the left femoral artery with the paw ligated as described earlier, and the cutaneous blood flow from the paw in the right great saphenous vein. We isolated the greater part of the thigh and lower leg muscles of the right leg by applying mass ligatures and by liga-

tion of the lateral branches from the right iliac and right femoral arteries. Under these conditions, when the blood pressure in the paw arteries was presumably only slightly below the recorded systemic blood pressure, we observed a marked increase of the cutaneous circulation after injection of Triurol, for in this case there could not have been a redistribution of blood such as that in the preceding experiment, where a reduced blood flow in the paw was observed.

Discussion

Assuming that the compounds employed contain no other impurities than those stated in the formula — which question mostly concerns Triurol, and according to its manufacturers there is no evidence that it does — the conclusion must be that in Triurol we have a substance which, in the concentrations we used, has a very powerful vascular action. Although Hypaque qualitatively has a similar effect, it is only a very slight one. It is interesting to note that a minor change in the molecular structure from a monoacetylamino to a corresponding diacetyldiamino compound has caused these major differences in the pharmacologic properties. Both substances, however, have an exceptionally low toxicity (LD_{50} for mice is reported to be 6 to 12 g/kg).

At the present time there is no possibility of drawing any definite conclusions regarding a causal relationship between the effects observed here and differences in the side-effects which have been noted between the two compounds in clinical series or in other types of experiments. Broadbridge (1956), for instance, reported that Hypaque produced fewer side-effects than Diaginol (sodium acetrizcate) in cerebral angiography. One effect of the latter agent was a subjective sensation of heat, which may have been due to the vasodilator action we have described. Idbohrn (1957) in an experimental study on injuries caused by contrast media in hydronephrotic kidneys, found that Triurol produced greater parenchymal damage than did Hypaque. A similar difference between Triurol and Hypaque as regards vascular damage in the kidneys after renal arteriography has been observed by one of us. This will be discussed in a later paper, as well as the interesting fact that Triurol as a rule caused a decrease in the renal blood flow.

In most of our experiments we unfortunately used Hypaque 45 % and Triurol 50 % a fact which, on comparison of the effects in a single experiment, is calculated to give a somewhat erroneous idea since the two solutions are not fully comparable. Hypaque has both a higher molecular weight and a lower concentration, and accordingly the molecular concentration is less than that of Triurol; for with regard to the molecular concentration Hypaque 45 % approximates Triurol 41 %. This possibility of

misinterpreting the results will be eliminated, however, if the latter are presented in the form of dose response curves, as in our diagram. It is here evident that a very distinct difference exists between the pharmacologic effects of the two substances.

The doses employed must be regarded as fairly small. Calculated on the basis of total body weight, 0.05 ml in a cat is roughly equivalent to 1 ml in man. The dose clinically employed in femoral arteriography is substantially greater, usually 10 to 20 ml. In aortography and angiocardiography, considerably higher doses are given. It seems plausible to assume, therefore, that circulatory phenomena similar to those described may arise from arteriography with sodium acetrizoate in human subjects. At all events this effect may be a contributory cause of the fall in blood pressure observed by several authors in connection with roentgen examinations of this type. RICHARDSON and ROSE (1950), for example, found an average fall of 12 mm Hg in the systolic blood pressure on intravenous injection of 25 ml Urokon (sodium acetrizoate) 30 % for urography.

We would emphasize, however, that the relevant vasodilator effect of Triurol is not necessarily a drawback; on the contrary, in arteriography of, say, an extremity with poor circulation it may be very useful to know that the contrast medium at all events has no vasoconstrictor effect.

A substantial depression of the peripheral resistance, if involving a large part of the body, is bound to place a heavy strain on the blood pressure regulating mechanisms of the organism.

The reports in the literature concerning the vascular effects of contrast media are, as pointed out above, somewhat contradictory. Many authors postulate, for instance, that a substance has a vasoconstrictor effect simply because they have observed a reduced blood flow, etc. Such a conclusion will be justified only if the experimental conditions are so well controlled that other hemodynamic variables are kept constant or are directly measured. Thus it is almost impossible to evaluate the vascular effects of the substance on intravenous administration, as many authors unfortunately do; the complex interaction of different factors — the heart, peripheral resistance, vasomotor reflexes, central vasomotor tone, etc. — makes interpretation of the results extremely difficult, particularly if the blood pressure is the only factor observed. An example of decreased blood flow following intra-arterial injection of an agent with an unequivocal vasodilator action was cited above in the section dealing with the effect of Triurol upon cutaneous vessels. In this connection it is worthwhile mentioning that SHAW (1956) observed a diminution of the blood flow in the toes (in performing plethysmography of the great toe in man) on injection of Diodrast and Urokon into the femoral artery. According to the results now presented, SHAW's observations do not necessarily imply that those contrast media have a vasoconstrictor effect in the great toe; they could be attributable to hemodynamic factors.

The assumption that the vascular paralysis, which Triurol causes to such a greater degree than does Hypaque, is due to a direct action on the smooth-muscle cells does not conflict with the earlier literature. A similar hypothesis was propounded by *e. g.* GORDON, BRAHMS, MEGIBOW and SUSSMAN (1950), who reported a fall of blood pressure and vasodilatation following the injection of Diodrast. They found that 'the Diodrast reaction' was unaffected by epinephrine, neosynephrine, pitressin, atropine, vagotomy, tetraethylammonium, and histamine antagonists. The major difference in response between the two chemically closely related substances which we investigated lends support to the idea of a chemo-toxic action of the compound per se. Further, the investigations of BROMAN and OLSSON (1948, 1949) into the effect of contrast media on the blood-brain-barrier have demonstrated that the majority of such media serve to increase the permeability. This also applies to sodium acetrizoate, which was recently studied by those authors (1956). In the opinion of BROMAN and OLSSON (1949) the relevant effect is largely due to a direct chemo-toxic action on the endothelial membrane of the vascular wall. As regards this chemo-toxic action on the blood-brain-barrier WHITELEATHER and DESAUSURE (1956) have recently compared iodopyracet (Diodrast), sodium diatrizoate (Hypaque), and sodium acetrizoate (Urokon). They found that there was a great difference between these contrast media: Urokon caused a higher incidence of damage than Diodrast and Hypaque.

Acknowledgement

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SUMMARY

In experiments in cats the systemic blood pressure and the blood flow in skeletal muscle, intestine and skin were recorded after intra-arterial injections — similarly to peripheral arteriography — of two tri-iodo-benzoic acid derivatives, sodium acetrizoate (Triurol) and sodium diatrizoate (Hypaque). Sodium acetrizoate gave rise to marked vasodilatation and increase in blood flow for a duration of 10 to 15 minutes. It had the same effect on both muscle vessels and cutaneous and intestinal vessels. Sodium diatrizoate produced a moderate increase in the blood flow of some 1 to 2 minutes' duration and its vasodilator effect, moreover, was much smaller than that of sodium acetrizoate. The vasodilator action is attributed to a direct chemo-toxic effect.

ZUSAMMENFASSUNG

Bei Katzen wurde experimentell der Körperblutdruck und die Strömungsgeschwindigkeit des Blutes in der Skelettmuskulatur, im Darm und in der Haut nach intraarterieller Injektion — ähnlich wie bei der peripheren Arteriographie — von zwei Trijodbenzoësäure-

derivaten. Triurol (Natriumazetriozat) und Hypaque (Natriumdiatrizoat) gemessen. Triurol veranlasste eine markierte Vasodilatation und einen Anstieg der Strömungsgeschwindigkeit des Blutes für 10 bis 15 Minuten. Es wirkte auf die Gefässe der Muskulature, der Haut und des Darmes gleichartig. Hypaque erzeugte einen mässigen Anstieg der Blutströmungsgeschwindigkeit während etwa 1 bis 2 Minuten und weiterhin war der vasodilatatorische Effekt viel geringer als der des Triurols. Die vasodilatatorische Wirkung ist an einen direkten chemisch-toxischen Effekt gebunden.

RÉSUMÉ

Au cours d'expériences sur des chats, les auteurs ont enregistré la pression sanguine systémique et le débit sanguin dans les muscles squelettiques, l'intestin et la peau, après des injections intra-artérielles — comme pour l'arteriographie périphérique — de deux dérivés de l'acide tri-iodo-benzoïque, l'acetrizoate de sodium (Triurol) et le diatrizoate de sodium (Hypaque). L'acétrizoate de sodium a donné lieu à une importante vasodilatation et à une augmentation du débit sanguin d'une durée de 10 à 15 minutes. Il a eu le même effet sur les vaisseaux des muscles et sur ceux de la peau et de l'intestin. Le diatrizoate de sodium n'a produit qu'une augmentation modérée du débit sanguin durant environ 1 à 2 minutes, et, en outre, son effet vasodilatateur a été beaucoup plus faible que celui de l'acétrizoate de sodium. Cette action vasodilatatrice est attribuée à un effet toxique chimique direct.

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HYPERVASCULARIZATION IN CHRONIC INFLAMMATION DEMONSTRATED BY ANGIOGRAPHY

Angiographic, histopathologic, and microangiographic studies

by

Curt Lagergren, Åke Lindbom and *Gunnar Söderberg*

During the last ten to fifteen years angiography has been used to an increasing extent, notably in the diagnosis of cerebral tumours, and it has also long been a diagnostic aid in extracranial neoplasms. In the opinion of most authors who have reported their findings in this field, the hypervascularization demonstrable in some tumours points to malignancy. Little attention has been paid, however, to the question of the angiographic differential diagnosis between a tumour and an inflammatory process.

In the arteriographic examinations of four cases of probable tumour we found hypervascularization which on histologic investigation proved to be due to chronic inflammatory processes.

Earlier angiographic investigations. Since the early reports of DOS SANTOS, LAMAS and CALDOS (1931) and DOS SANTOS (1934), numerous authors have published their experiences in angiography of peripheral

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tumours (FARIÑAS, REBOUL and RACINE, et al.). Many sarcomatous tumours are highly vascular. In typical cases the arteries supplying the affected area are dilated and increased in number, and within the tumour itself and particularly its periphery an irregular vascular network of pathologic vessels is seen. The veins passing from the tumour region are contrast-filled during the arterial phase due to an arteriovenous shunt.

Only a few angiographic findings in inflammatory processes have been reported. DOS SANTOS (1950) wrote that osteomyelitis cases 'always show a relative ischemia at the level of the bone lesion'. MUCCHI and COLUMELLA reported 'slight slowing of the circulation' and that 'synovial involvement leads to increased arterial and venous flow in the membrane' in osteomyelitis; in tuberculosis the blood supply was diminished, and in syphilis they sometimes found ischemia and, in one case, 'increased circulation'. VOGLER (1955) observed no increased vascularization in inflammatory processes of bone. In two cases of 'low-grade pyogenic abscess involving bone', SUTTON found no hypervascularization. Nor was the latter condition demonstrable in a case of osteomyelitis of the tibia reported by PAPE and SEYSS.

Rapid passage of blood from the arteries to the veins occurs in the region of chronic varicose leg ulcers. This was shown angiographically by VOGLER (1953); we have ourselves made similar observations in arteriographic examinations of ulcers of the legs.

Inflammatory granulation tissue with special reference to vascularization. The vascular changes associated with acute inflammation are customarily divided into two stages. These changes have been described by JOSEPH LISTER (1855), who observed vascular reactions in a frog's foot microscopically after the application of hot water '... at first an enormously increased flow of blood: the capillary network becoming far more red than natural, and each capillary coming to admit three or four blood corpuscles abreast instead of only one... Later, the capillaries became distended and stuffed with red corpuscles, and the blood was first retarded, then stagnant.'

In chronic inflammation the vascular changes are in the main similar to those accompanying acute inflammation, though of less degree and often obscured by reparative processes (WILLIS, MACCALLUM). Chronic inflammatory granulation tissue contains numerous capillaries in a loose network of stellate connective tissue cells. There is interstitial infiltration of round cells (lymphocytes, plasma cells, and histiocytes) and sometimes of leucocytes. With a subsidence in the inflammatory condition the free cells disappear; the capillaries become obliterated and collagen fibrils and fibers appear. The granulation tissue, initially highly vascular and cellular, ultimately shows a paucity of vessels and cells (ASCHOFF, HUECK).

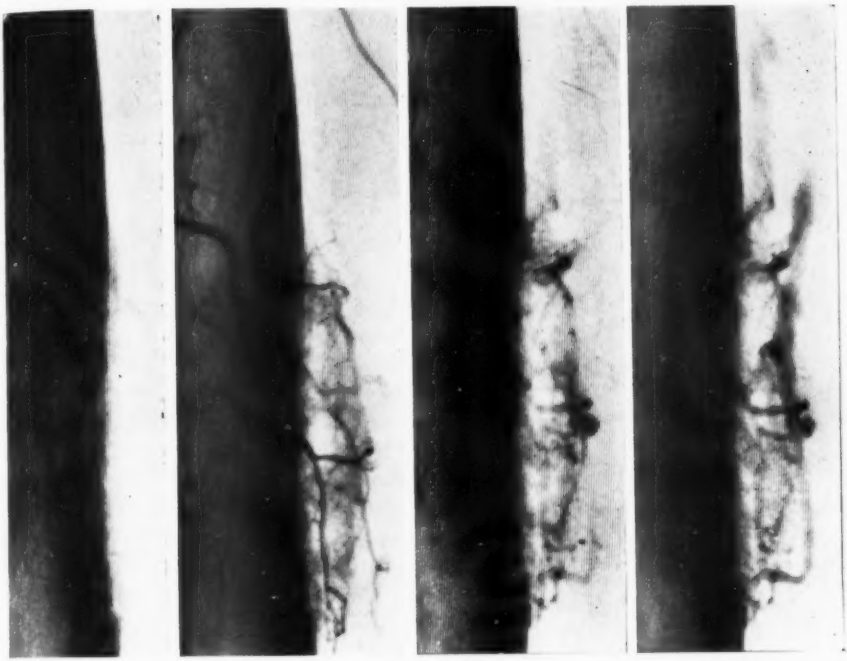

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Fig. 1. Case 1. Metastasis in femur from bronchial squamous-cell carcinoma. a) Destruction of cortex of femur. b) Early arterial phase. Marked increase of vessels around lesion. c) Late arterial phase. Venous filling in vicinity of focus. d) Venous phase. Relevant efferent veins well filled.

Studies of living granulation tissue (CLARK et coll.) in transparent chambers placed in holes punched through the ears of rabbits showed that the new vessels grew first as small buds of endothelial cells which then became canalized and sanguiferous; the endothelial ducts became differentiated to arterioles and small veins. These vessels were reported to be highly 'plastic' and undergoing structural modifications on thermal or mechanical irritation or changes in blood flow. The formation of vessels in inflamed tissue probably occurs more or less in the same way. The small blood vessels surrounded by inflammatory cells may also well be 'plastic', *i. e.* varying in calibre and differentiation according to the degree of irritation.

Round-cell reaction in malignant tumours. EWING and WILLIS reported that lymphocytes, plasma cells, and occasionally leucocytes, appear in or

Fig. 2. Post-mortem arteriogram. Decalcified section through metastasis and surroundings. Zone of dense vessels in medullary cavity along an almost avascular metastasis.

around malignant tumours, as for instance mammary carcinoma and squamous carcinoma of the lips, tongue, skin, and uterine cervix. WOGLOM presented a critical review of papers on immunity to transplantable tumours, from which it emerges that a number of investigators have observed lymphocytes and plasma cells around malignant neoplastic tissue in experimental animals.

Present material

About 150 cases of tumours and suspected neoplastic processes, chiefly in the extremities, have been examined arteriographically in our roentgen department since 1941. From these we have selected 4 cases which, both clinically and arteriographically, were thought to be cases of malignant tumours but in which the histologic examination revealed inflammatory processes. In 3 of these cases the catheter method of SELDINGER was used and contrast medium injected in the proximity of the morbid process so that the blood vessels were contrast-filled. In the fourth case the contrast medium was injected via a puncture needle directly in the artery. Serial arteriograms were obtained at intervals of about 2 seconds in all cases.

Histologic specimens were obtained at the resection of a joint in 1 case, at biopsy in 2, and at autopsy in 1 case. In no case was radiotherapy given. The sections were prepared with a conventional histologic technique. Biopsy material from 7 cases of varicose leg ulcers was also studied, but these cases were not examined arteriographically. For the arteriographic appearances of ulcers of the leg, reference should be made to VOGLER.

One of the four first-mentioned cases had a metastasis of the femur and was subjected to post-mortem arteriography with a contrast medium containing barium sulphate (Micropaque), which penetrated into the capillaries but did not enter the veins. The specimen was sawn into sections about 0.5 cm thick and selected areas were examined histologically. The same zones were also examined by means of a microarteriographic technique which, with the use of extremely fine-grained emulsion and satisfactory beam geometry, gave a resolution that permitted studies of vessels with calibres of down to 30 microns (BELLMAN).

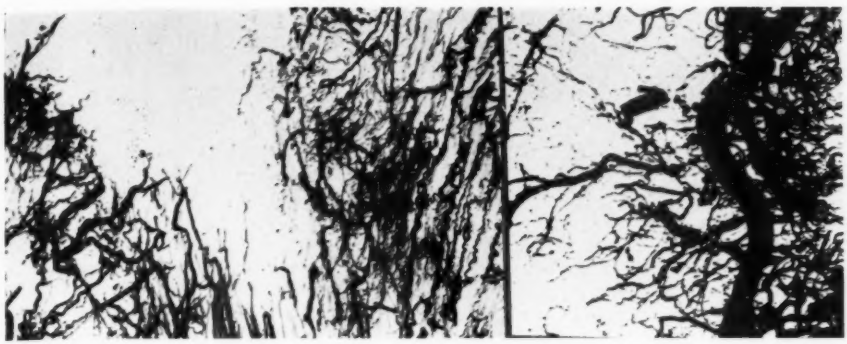

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Fig. 3. a) Microarteriogram of region at distal part of metastasis which corresponds to the white triangular area. Highly increased vascularity in surrounding zone; some small arteries have a spiral course like collaterals. × 9. b) Microarteriogram of densely arranged vessels in and adjacent to round-cell infiltrated zone surrounding metastasis. Diameter of large artery about 500 microns; the vessels at border of avascular region (right) mostly 30 to 100 microns. × 7.

Case reports

Case 1. Cancer metastasis of the femur surrounded by round-cell infiltration. Man, aged 66, with pain in thigh. Roentgenograms showed an area of destruction in the femoral shaft. At arteriography, hypervascularization was found in that zone (Fig. 1). Patient died suddenly after a few days. Autopsy disclosed bronchial carcinoma with multiple metastases; the metastasis in the cortex of femur was surrounded by copious round-cell infiltration. The primary tumour was a moderately to somewhat poorly differentiated squamous carcinoma. Death was probably due to pulmonary embolism.

Case 2. Chronic tenosynovitis of forearm. Man, aged 54, with swelling and tenderness over the dorsal tendon sheaths of wrist after agricultural labour. A similar condition twelve years before had been regarded as tendovaginitis. Arteriography showed hypervascularization (see Fig. 5). At biopsy there was no appreciable bleeding. Histologic examination pointed to chronic tenosynovitis.

Case 3. Chronic periostitis of ulna. Man, aged 32, with swelling of forearm. Roentgenograms showed periosteal reaction of the ulna, several millimeters thick and 10 cm long. At arteriography the affected area was found to be highly vascular (Fig. 6). Biopsy disclosed an inflammatory process. Patient recovered from this condition but died from nephritis three years later. At autopsy no pathologic changes were found at the site of the earlier ulnar lesion.

Case 4. Chronic monarthritis of the hand. Man, aged 40, with swelling and tenderness over the third metacarpophalangeal joint. Arteriography revealed periarticular hypervascularization. To improve the function of the hand the joint was resected, its capsule proving to be distended and nodular on the inside. Histologic examination disclosed hypertrophic synovial villi with lymphocyte and plasma-cell infiltration, fibrinoid necrosis, and granulomas, as in rheumatoid arthritis. No other joints were involved.

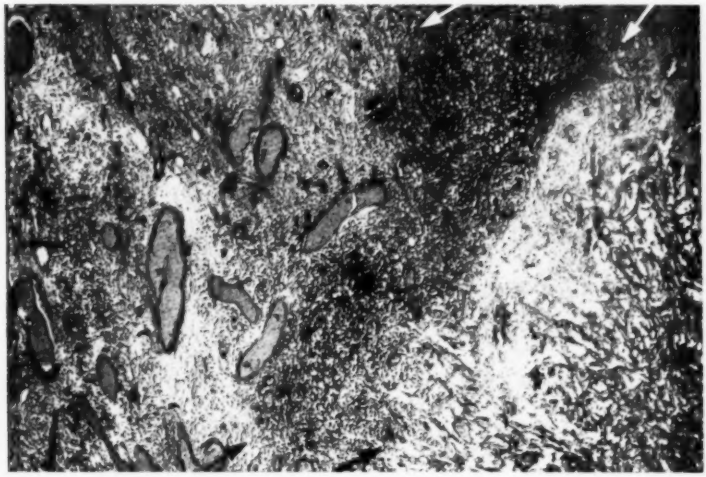

Fig. 4. Photomicrograph of border of femoral metastasis. Arrows indicate zone of round cells. To the right, avascular metastasis. To the left, adjacent to zone of round cells, contrast-filled capillaries, attaining a width of about 100 microns. × 36.

Histopathologic findings

Each of the 11 cases had chronic inflammatory changes with infiltrations composed chiefly of lymphocytes and plasma cells (round cells). In the areas most densely infiltrated with round cells the ground tissue was loose and of granulation type, with a sparse network of connective-tissue cells, in the interstices of which were the inflammatory cells showing perivascular accumulation. Small blood vessels were fairly numerous in the vicinity of the round-cell infiltrations; they were mainly of normal diameter, but an appreciable number with thin walls had quite large calibres. In Cases 2 and 4 (of synovitis) for instance, small areas in the histologic sections contained blood vessels with diameters of 50 to 100 microns, the walls of which were not differentiated more conspicuously than the capillary type (Fig. 8).

In the round-cell infiltrated zone surrounding the femoral metastasis were a moderate number of blood vessels, some contrast filled, having diameters of 50 to 100 microns and thin walls of the capillary type or showing only very slight differentiation with intramural fibroblasts (Fig. 4).

In histologic preparations from the leg ulcers the ulcer floor had a zone of granulation tissue 1 to 2 mm wide with round-cell infiltrations and groups of capillaries, mostly of normal calibre but occasionally with lumina

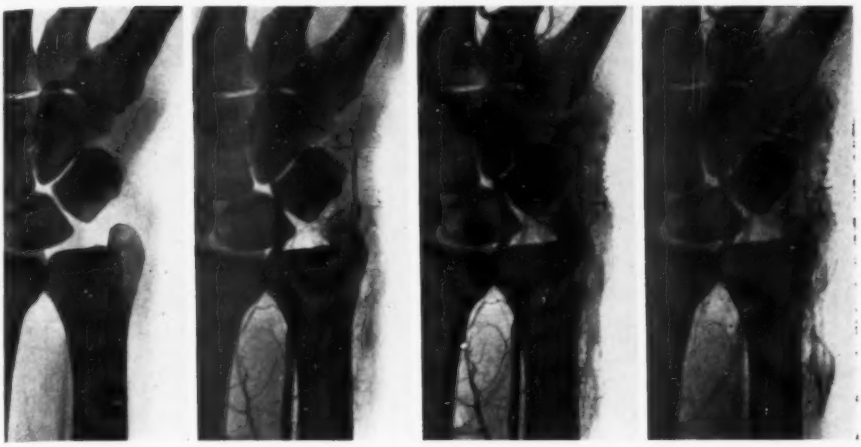

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Fig. 5. Case 2. Chronic tendovaginitis at wrist. Serial arteriography. Hypervascularization and arteriovenous shunt. a) No vessels filled. (Small amount of contrast medium in ulnar artery.) b) Early arterial phase. Numerous minute arteries filled along tendon, especially at styloid process of ulna. Adjacent to the ulnar metaphysis 'blush' in synovial tissue caused by filling of vessels of fine calibre. c) Middle arterial phase. Numerous small veins surrounding lesion are well filled and large veins are filling. d) Late arterial phase. Many veins well filled.

of up to 20 to 30 microns (Fig. 7a). In some of the sections from the leg ulcers a highly vascular zone was also observed in the firmer fibrous connective tissue outside the ulcerated and infiltrated area (Fig. 7b).

Angiographic findings

The arteries round the affected zones were in all cases dilated — in Case 1 very markedly (Figs. 1, 5, and 6). Greater numbers of fine arteries were discernible in the relevant zones than in adjacent comparable regions. Probably this was due in part to dilatation of existing vessels, many of which thus exceeded the finest detectable calibre. In the zones in question the contrast medium passed into the veins far more rapidly than in adjacent tissues; it was already entering some veins while the fine arteries were still filled. The efferent veins, however, were not appreciably dilated (Figs. 1, 5, and 6). In no case was the shunt through the pathologically changed area as marked as that found in some sarcomas containing large pathologic vessels (DOS SANTOS, et al.). In Cases 2 and 4 the diseased tissue had, during the passage of contrast medium through it, a much denser appearance than the surrounding region, although no individual vessels were distinguishable (Fig. 5).

a b c d

Fig. 6. Case 3. Chronic periostitis of ulna. a) Thick layer of dense periosteal bone along shaft. b) Arteriogram, early phase. Numerous small vessels in layer along newly formed bone. c) Arterial phase, a few seconds later. Veins (arrows) already filled, indicating arterio-venous shunt.

At the post-mortem angiography with a conventional roentgen technique (non-screen film), a decalcified section through the femur showed a greatly increased arterial supply round the metastasis, which itself was almost avascular (Fig. 2). In microangiograms the arteries were observed to increase substantially towards the zones where, in corresponding histologic sections, the round-cell infiltrations outside the metastasis were localized (Fig. 3a, b). In and contiguous to these zones were densely packed vessels with calibres of up to 100 microns. Some of the arteries in the environment were tortuous, like collaterals, but had regular lumina; they showed none of the variations in calibre that characterize pathologic vessels in sarcomatous tumours. Vascularization was maximal in the region of the round-cell infiltrated zones but very sparse in the metastasis itself (Fig. 3a).

Discussion

Hypervascularization is found in a number of chronic inflammatory conditions of varying localization and etiology: synovitis, periostitis, varicose leg ulcers, and round-cell infiltrations adjacent to carcinomas growing in bone. In the present cases angiograms revealed that the vessels surrounding the lesions were dilated and increased in number, and that the arterio-venous passage was accelerated.

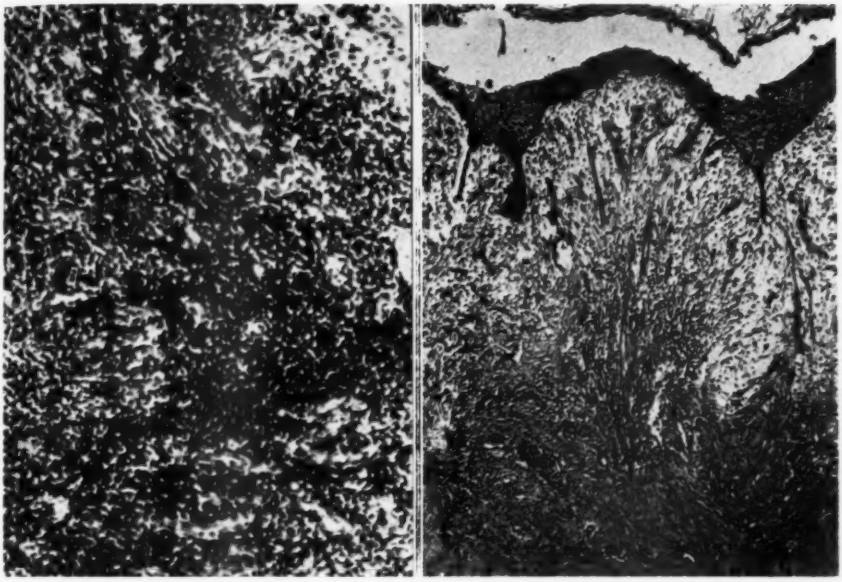

Fig. 7. Photomicrograph. Chronic varicose ulcer of leg. a) Marked round-cell infiltration of tissue with dense capillaries in floor of ulcer. b) Healed region just outside ulcer. Slight round-cell infiltration with dense capillaries arranged like a fountain. × 110.

Common to all these cases of varying etiology and localization was, as shown by the histologic findings, granulation tissue containing profuse round-cell infiltrations and densely arranged capillaries, some of them wide. From the case which was examined microangiographically and in which the infiltrations surrounded a carcinoma metastasis in bone, it is clear that the rapid passage of contrast medium from the arteries to the veins was localized to the highly vascular zones infiltrated by round cells. The vessels therein had, in the histologic sections, calibres equal to ordinary capillaries and greater (up to 50 to 100 microns). The microangiograms also showed numerous vessels of about the same calibres in these zones. The swift arterio-venous passage is likely, therefore, to take place chiefly via these abundant wide, probably new, capillaries in and around the round-cell infiltrations. In view of the similar histologic structure in all these cases of infiltrated, highly vascular tissue, the shunt mechanism might also well be identical. In such chronic inflammatory processes the blood circulation through the tissue is thus increased.

The microangiographic and histologic findings accordingly suggest that in these chronic inflammatory processes, contrast medium passes from the

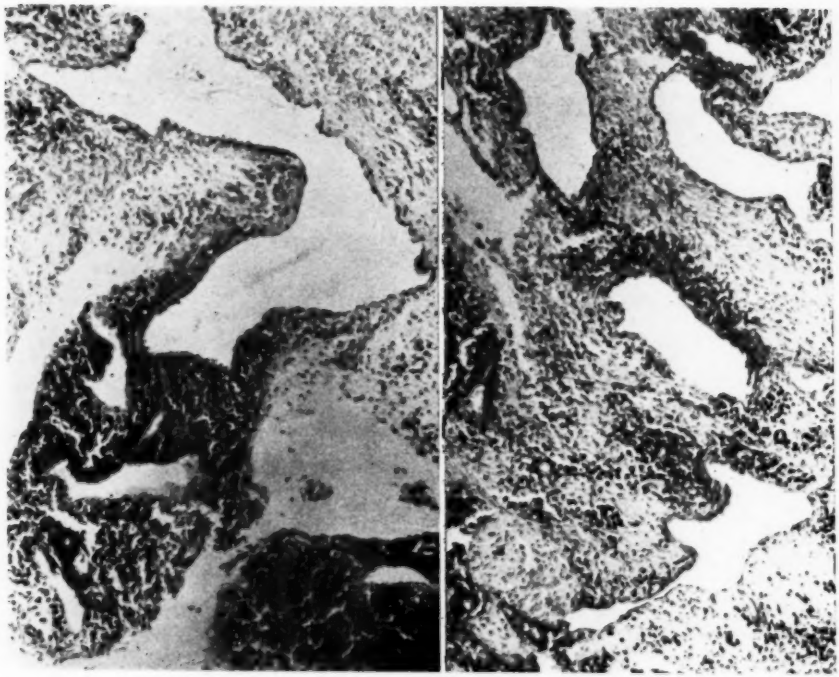

Fig. 8. Case 4. Chronic synovitis (monarthritis of metacarpophalangeal joint). Wide vessels of capillary type in round-cell infiltrated synovial membrane with villous hyperplasia. Round cells often showing perivascular arrangement. × 130.

arteries to the veins mainly through vessels with diameters of less than 100 microns. Arteriographically demonstrable arterio-venous shunts may thus take place both via large-calibre vessels in tumours (DOS SANTOS et al.) and via an increased number of large capillaries in inflammatory processes. With the conventional arteriographic technique, vessels having diameters of less than about 300 microns cannot be shown (MATTSSON); the roentgenographic study of finer vessels requires a special microtechnique that cannot be used in clinical material. When therefore an angiographically demonstrable arterio-venous shunt occurs through vessels below the limit of detectability (300 microns) such vessels cannot be evaluated by the conventional technique; not until the pathologic vessels exceed the above limit will a purely angiographic differentiation between tumour and inflammatory process be possible. When angiograms disclose a highly vascular process through which shunts occur from arteries to veins, they may not therefore enable the examiner to decide if a tumour or an inflammatory lesion is present.

Our experience with angiography of malignant tumours of the extremities suggests, however, that irregular pathologic vessels of varying calibre are usually discernible in the angiograms, particularly in the case of sarcomas; hence this method of examination, notwithstanding the above-mentioned limitation, often yields useful information.

Judging by our histologic investigations, the arterio-venous shunt that takes place in the region of varicose leg ulcers is probably due to chronic inflammation in the ulcer floor. Two of our cases (Cases 2 and 4) had chronic inflammation of synovial tissue, which in one of them was highly vascular; MUCCHI and COLUMELLA also observed hypervascularization in cases of chronic osteomyelitis with synovial involvement. Owing to the tendency of synovial tissue to react with round-cell infiltrations and increased vascularity, marked hypervascularization may sometimes be found angiographically in the region of joints and tendons. It is therefore not necessarily a sign of tumour; it will more often probably be due to an inflammatory process.

Conclusions

Chronic inflammatory processes are sometimes associated with marked hypervascularization that can be demonstrated arteriographically.

In and contiguous to the affected zones the arteries are dilated and contrast medium passes from arteries to veins much faster than in the surrounding tissues. This arterio-venous shunt probably occurs via large capillaries with diameters not exceeding 100 microns.

Angiographically discernible hypervascularization is not, therefore, pathognomonic of tumours. If, at arteriographic examination, pathologically changed tissue is highly vascular and contrast medium passes swiftly to the veins but no abnormal vessels can be observed in the affected area, angiographic differentiation between tumour and inflammatory process may not be possible.

Hypervascularization detected in skeletal metastases from carcinoma may be due to the round-cell infiltration that in some cases surrounds the tumour.

Arterio-venous shunts in varicose leg ulcers probably result from the chronic inflammation therein, and thus have the same etiology as similar shunts in other chronic inflammatory conditions attended by hypervascularization.

SUMMARY

The authors describe and discuss four cases which were considered both clinically and arteriographically to be neoplastic processes but in which the histologic examination revealed inflammatory processes. These were selected from a material of 150 cases of tumours examined arteriographically.

ZUSAMMENFASSUNG

Die Verfasser beschreiben und diskutieren die Befunde in 4 Fällen, die sowohl klinisch als auch arteriographisch als maligne Prozesse aufgefasst wurden, in denen aber die histologische Untersuchung entzündliche Veränderungen ergab. Die Fälle sind einem Material von 150 arteriographisch untersuchten Tumoren entnommen worden.

RÉSUMÉ

Les auteurs présentent et analysent quatre cas considérés cliniquement et artériographiquement comme des processus néoplasiques, mais où l'examen histologique a révélé des lésions inflammatoires. Ces cas proviennent d'une série de 150 cas de tumeurs examinés artériographiquement.

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POST-TRAUMATIC INTRA-UTERINE SYNECHIAE

by

P. Bergman and *L. Wehlin*

Damage to the endometrium is capable of causing permanent changes of varying severity and in advanced cases may result in obliteration of the uterine cavity (NETTER et coll. 1955) or occlusion of the cervix and isthmus (STAMER 1946, HALD 1949). Amenorrhoea may then cause the patient to seek advice. The diagnosis can usually be made by exploration with a uterine sound.

A further group of cases in which damage has led to deformation of the uterine cavity or to intra-uterine adhesions may also be recognized. These are known under the common name of intra-uterine synechiae and have been described by ASHERMAN and NETTER. The diagnosis cannot be made without the help of hysterography. Intra-uterine synechiae are important because of their causal relationship to hypomenorrhoea or amenorrhoea, dysmenorrhoea, repeated abortions and sterility. They mostly occur in patients in whom the endometrium has been damaged by puerperal curettage or evacuation after abortion. Voices have long been raised against the use of sharp instruments during pregnancy because of the risk of perforation. The risk of endometrial injury with the subsequent development of intra-uterine synechiae is another reason for avoiding such instruments.

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Material

The material consisted of 11 cases of post-traumatic intra-uterine synechiae, 4 (Cases 1, 2, 3, and 4) of which were verified at operation. The remaining 7 cases were not operated upon and therefore no such confirmation was available. The histories and the roentgen findings in these cases agreed well, however, with those in the morphologically verified group, and the clinical examinations suggest no other explanation for the hysterographic changes.

Case reports

Case 1. M. J., aged 42 years, had her first child in 1938; owing to profuse bleeding, 'blunt' curettage was performed one month after delivery and abundant placental rests were removed. In 1946 she was investigated for sterility and hysterography showed a rounded formation in the middle of the uterine cavity, which was then interpreted as being a polyp. Curettage indicated a normal endometrium in the secretory phase, but no polyps. In 1957 she returned because of painful and difficult menstruation and several myomata were found.

Hysterography in 1957 (Fig. 1, a and b) showed two large synechiae, one in the middle and a smaller one on the left side of the body of the uterus; the tubes were patent. The uterus was removed. The operative specimen confirmed the hysterographic findings from 1946 and 1957. An extensive synechia was present between the ventral and dorsal walls of the uterus (Fig. 1 c) with small adhesions in the left aspect of the uterine cavity. Microscopic examination of the synechia disclosed myometrial fragments lined with endometrial mucosa. Changes characteristic of adenomyosis were noted in the synechia as well as in the uterine wall.

Case 2. I. E., aged 23 years, had her first child in 1953. 'Sharp' curettage was performed 17 days after delivery because of profuse bleeding. Eight months after delivery the patient was admitted and again subjected to curettage for prolonged irregular bleeding. An occlusion was noted 4 cm up the cervix and when an attempt was made to pass a sound and dilate the latter, the urinary bladder was perforated, this being confirmed by cystoscopy; the cervico-vesical fistula closed spontaneously. The patient then had alternating spells of amenorrhoea and dysmenorrhoic bleeding and in 1957 came up complaining of sterility.

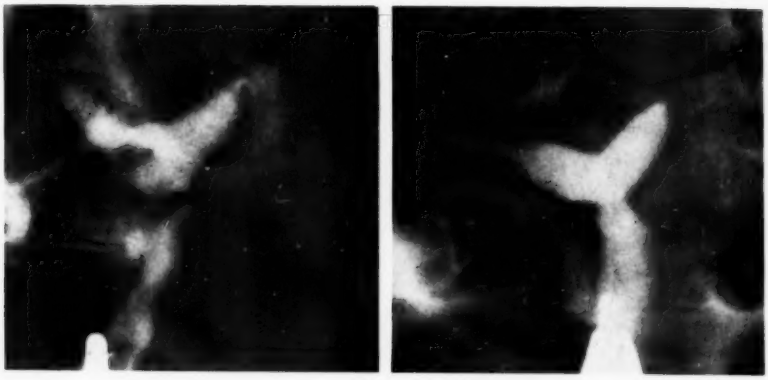
Hysterography (Fig. 2 a) showed two well-defined synechiae in the corpus; the tubes were patent. Because of her history of perforation abdominal hysterotomy was performed. The hysterographic appearances were confirmed. The synechiae were loosened manually and the cervix was dilated from above. A plastic tube extending from the fundus through the cervix to the vagina, was inserted to prevent the development of further adhesions in the uterine cavity; it was fastened in the portio and left in situ for a month. After operation, the menstrual flow, which had previously been scanty became normal and no longer painful. Post-operative hysterography (Fig. 2 b) showed a uterine cavity of normal size and almost normal outline; the tubes were patent.

a b c

Fig. 1. Case 1.

a) and b) Preoperative hysterography. Two large synechiae, one in the middle and one on the left side of the body of uterus. c) Specimen.

Case 3. H. L., aged 28 years, had her first child in 1952, and two weeks after delivery was subjected to 'blunt' curettage for profuse bleeding. The procedure yielded abundant placental rests and microscopy also showed myometrial fragments. The patient was then amenorrhoic for long periods. In 1955 she came up complaining of sterility and received hormonal substitution therapy; she then had an abortion, this being repeated in 1956.



a b

Fig. 2. Case 2. a) Preoperative hysterography. Two synechiae in the corpus. b) Postoperative hysterography 5 months after manual loosening of synechiae.

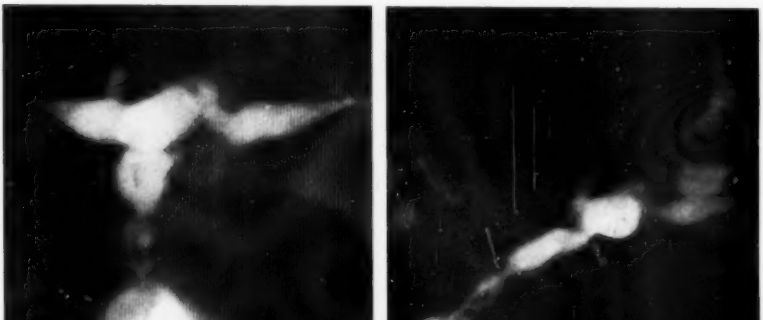
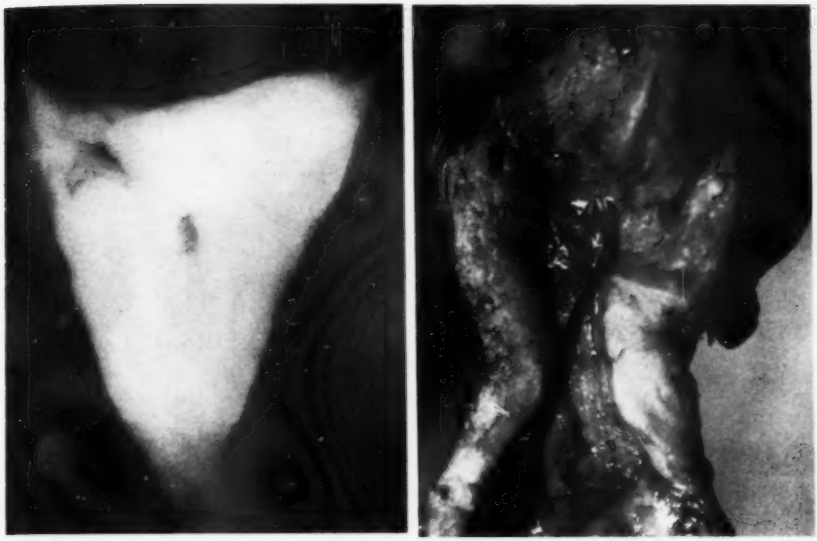


Fig. 3. Case 3. Hysterography. Uterine cavity deformed by synechiae.

Hysterography (Fig. 3) in 1956 showed synechiae giving the uterine cavity a deformed and irregular appearance; the tubes were patent. In 1957 the patient was delivered by caesarean section because of placenta previa. The operation was performed only 10 days before the calculated term but the infant weighed only 1,990 g. Despite this the child did not show the ordinary signs of immaturity, and its subsequent development was normal. The placenta was divided up into several portions held together by the membranes with anastomosing blood vessels. One portion of the placenta, the size of the palm of the hand, was attached to the fundus and a similar portion lay just above the internal os; in addition there were some 10 small bi-placentae attached to different parts of the uterus. The various placental fragments were firmly attached to the uterine wall and were difficult to loosen. The uterine cavity was very irregular.



a b

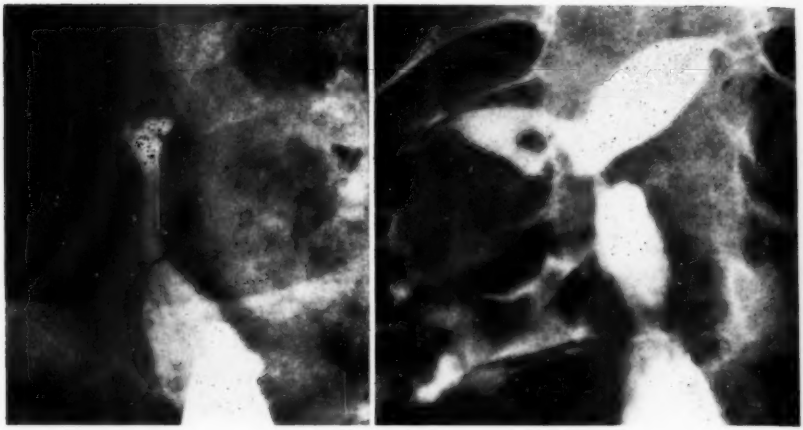
Fig. 4. Case 4. a) Hysterography of a specimen. Synechiae in the right horn and in the middle of the corpus. b) The instrument inserted in the specimen. A synechia is seen where the instrument is inserted in the specimen.

Case 4. V. K., aged 45 years, had her first child in 1943, followed by two abortions, one in 1955 and one in 1957. Curettage was performed on both occasions the second showing endometrial as well as myometrial fragments. One month after the last abortion the uterus was removed because of a large myoma.

Hysterography of the operative specimen in 1957 (Fig. 4 a) showed synechiae in the right horn and middle of the corpus. The second of these was well defined; the one in the uterine horn was irregular, being defined in some regions and diffuse in others. Examination of the operative specimen confirmed the hysterographic findings. The synechia in the body of the uterus is shown in Fig. 4 b; microscopic examination disclosed that it was built up entirely of endometrial mucosa. Signs of adenomyosis were noted in various parts of the cavity.

Case 5. S. O., aged 26 years, had her first child in May 1956. Both 'sharp' and 'blunt' curettage was performed 16 days after delivery for profuse bleeding. In December 1956 the patient came up complaining of scanty irregular bleeding at long intervals. The basal temperature curve was diphasic with normal cyclic rhythm showing that the ovarian cyclic function was normal. Despite this she was amenorrhoic for long periods and when bleeding recurred it was scanty and painful. Examination revealed an obstruction about 3 cm up the cervix. This was forced and the cervix dilated; the dysmenorrhoea was relieved.

Hysterography (Fig. 5 a) before the above procedure revealed that the lumen of the



a b

Fig. 5. Case 5. Hysterography performed a) before and b) two months after passing a sound and dilatation of cervix.

corpus was occluded about three centimetres up the cervix, and further hysterography performed following it showed a cavity deformed by synechiae in the right horn and middle of the corpus (Fig. 5 b); the tubes were patent.

Case 6. A. M., aged 33 years, had her first child in 1950. She had two abortions in 1953 and 1954 and on both occasions 'sharp' curettage was performed.

Hysterography in 1955 showed multiple well-defined synechiae of varying size in the middle of the corpus; the tubes were patent.

Case 7. C. P., aged 23, had her pregnancy legally terminated in 1932. Hysterographies were carried out in 1940 because of sterility and showed an irregular mass on the left side of the uterine cavity; this was then interpreted as being a polyp. As the changes appeared to be permanent, even after curettage, the patient underwent explorative hysterotomy in 1941 without anything of interest being found. Since uterine synechiae were not known at that time, it is quite understandable that manual exploration of the uterine cavity yielded negative results. Intra-uterine synechiae are sometimes soft and can readily be missed on instrumental or manual exploration. Two years later the patient became pregnant, this resulting in the birth of a living child at term (breech presentation); a retained placenta required freeing by hand.

Hysterography (Fig. 6) in 1940 showed an irregular formation on the left side of the uterine cavity which today would be interpreted as being a synechia. A small cavity of regular outline, possibly post-traumatic was filled upon the left side of the cervix; the tubes were patent.

Case 8. I. S., aged 40 years. Her first pregnancy terminated in abortion in 1933. 'Sharp' curettage was performed as some of the placental fragments were firmly adherent to the uterine wall.

Fig. 6. Case 7. Irregular formation, probably synechia on the left side of the uterine cavity. Not verified.

Fig. 7. Case 10. Synechia in the region of the isthmus extending in a band from the left, obliquely upwards to the right.

Hysterography in 1949 revealed an ill-defined synechia on the right side of the corpus. Two more rounded formations were seen in the region of the isthmus and were also interpreted as being synechiae; the tubes were patent.

Case 9. S. Z., aged 38 years, had normal deliveries in 1939 and 1942. Curettage was performed for dysmenorrhoea in 1951 and 1952 but on neither occasion did microscopy of the specimen show evidence of any abnormality.

Hysterography in 1954 showed extensive synechiae in the middle of the corpus; the tubes were patent. Further curettage suggested a normal endometrium; no polyps were found.

Case 10. E. B., aged 32 years, had had two normal pregnancies in 1942 and 1945. In 1950 she was examined because of metrorrhagia and secondary sterility. Hysterography showed no signs of any abnormality. From then on until 1956, when she was again examined hysterographically, the patient underwent curettage on 3 different occasions for recurrent menstrual disorders; the endometrium always appeared to be normal.

Hysterography (Fig. 7) in 1956 showed a well-defined synechia in the region of the isthmus, extending in a band from the left obliquely upwards to the right.

Case 11. M. B. A., aged 33 years had had 3 normal deliveries in 1943, 1945, and 1947. In 1953 and 1954 she underwent curettage for menstrual disorders; on both occasions the endometrium appeared to be normal.

Hysterography was then performed (1954) and showed an irregular synechia on the left side of the uterus close to the isthmus.

Fig. 8. Operative specimen. Pincette introduced below thin mucosal bridge, tip pointing towards a round mucosal defect in the middle of dorsal wall of uterus. Myoma underneath the defect. Patient submitted to curettage 5 months before extirpation of uterus.

Fig. 9. Operative specimen. Broad synechia between the ventral and dorsal walls. This synechia was widest dorsally. It extended from the posterior wall of the uterus, from a site where a myoma had been enucleated four years before.

Discussion

Intra-uterine synechiae are probably much more common than hitherto supposed. NETTER et coll. (1956) observed as many as 42 cases within 18 months. ASHERMAN published his first observation of intra-uterine synechiae in 1950; according to his latest publication (1957) he has now seen as many as 158 cases.

It is possible that the frequency of intra-uterine synechiae varies from one hospital to another. If so, it may depend on the frequency with which damage is inflicted during the puerperium or in association with abortion. Of the 11 cases described above, 4 had undergone curettage in the puerperium and 4 in association with abortion. As to the remaining 3 cases no information is available about any intervention likely to have caused injury except repeated curettage not related to pregnancy. Extensive uterine synechiae were seen in all the 8 cases in which curettage was performed during the puerperium or in association with abortion.

Of the 3 cases in which curettage was not related to pregnancy extensive synechiae were seen in 1 and less marked changes in the isthmus region in 2 cases.

Various symptoms cause these patients to seek advice. In our series of 11 patients 5 presented themselves because of secondary sterility. Known damage to the endometrium, especially in the puerperium or in association with abortion is sufficient to suggest synechiae. The occurrence of dysmenorrhoea, hypomenorrhoea, or amenorrhoea after such intervention strengthens the possibility. Unless the adhesions have resulted in occlusion of the internal os, which can be detected by the passage of a uterine sound, the clinical diagnosis of synechia requires the help of hysterography.

Typical synechiae appear in the films as well-defined formations bridging the uterine cavity. This bridging is best seen in films obtained perpendicularly to the synechiae, advisable in several projections (Fig.1b) As a rule the synechiae produce only slight or no deformation of the uterine cavity, although occasionally this may be marked (Fig. 3). Synechiae may be solitary or multiple and may involve any part of the uterine cavity. If they are situated in the cervix-isthmus region, they may lead to occlusion (Fig. 5 a). In none of our cases had the synechiae resulted in tubal occlusion.

It is sometimes difficult roentgenologically to differentiate synechiae from other intra-uterine conditions, especially submucous myoma and polyps and, though rarely, intra-uterine septa. A septum is, however, characterized by being always situated medially and appearing as a narrow strip (SCHULTZE and ERBSLÖH 1954). If the synechiae markedly deform the cavity (Fig. 3), it may be difficult to distinguish them from sequelae following endometrial tuberculosis. However, if the tubes are patent and of normal appearances there is no reason to suspect a tuberculous origin of the uterine changes.

There is general agreement on the cause of the changes. Since curettage in the puerperium and in association with abortion is the most common cause of post-traumatic uterine synechiae, more rigid indications and more careful performance of such curettages should decrease the risk of permanent uterine injury.

Curettage not related to pregnancy may also produce such injury (Cases 9, 10, and 11). If the uterine wall contains a myoma and the circulation is thereby disturbed it enhances the risks of injury to the endometrium. The myoma may provide a firmer support than that afforded by the surrounding tissue with the result that the curette may cut deeper in the area involved (Fig. 8). Of our 11 cases, however, only Cases 1 and 4 had a myoma. Apart from intra-uterine intervention, the enucleation of intra-mural myoma may result in the development of synechiae (Fig. 9).

It should be mentioned that in the 3 cases in which the uterus was removed, histologic examinations showed signs of adenomyosis in the synechia as well as in the endometrial lining elsewhere in the uterus. That the tissue ridges, *i. e.* synechiae, which had developed after intra-uterine damage, showed scattered endometrial islands was not unexpected. More remarkable was the fact that coexisting adenomyosis was seen elsewhere in the uterus. One is tempted to assume that the trauma that had led to the formation of synechiae had also caused this adenomyosis. Intra-uterine injury may thus be a factor in the causation of adenomyosis.

ASHERMAN's material contained some cases in which conception had occurred despite synechiae. He concluded that intra-uterine synechiae do not lead to sterility. Pregnancy may, of course, occur in the presence of intra-uterine synechiae, but this does not mean that such synechiae cannot decrease the chances of conception. Case 3 shows how nutrition of the fetus may be impaired when the endometrium has been damaged. In this case the placenta was split up into a number of small portions adherent to those parts of the uterus that had been damaged least. There is reason to suppose that the conditions for nidation in an injured endometrium are less favourable. The intra-uterine synechiae decrease the chances of endometrial implantation of the fertilized ovum and increase the risk of abortion. If pregnancy goes on to term such lesions increase the risk of complications during the latter half of pregnancy and delivery, *e. g.* malpresentation, placental retention, and placenta praevia (NETTER 1955).

ASHERMAN's series (158 cases) included 33 women who had become pregnant. In 21, pregnancy went on to term, in 6 it terminated in abortion and in 4 in premature delivery. Two of his patients were still pregnant at the time of publication of his material. The fact that pregnancy occasionally occurs and proceeds to term despite extensive synechiae contraindicates immediate surgical measures. In 2 of our patients pregnancy went on to term; in one of them pregnancy had been preceded by surgical intervention.

In the event of pregnancy, attempts should be made to loosen or remove the synechiae manually in association with abortion or delivery (ASHERMAN). If the patient has been sterile for a long time, operation must be considered. Case 2 shows how hysterotomy with manual division of the synechia is capable of producing a normal outline of the uterine cavity. In this case the patient obtained relief from dysmenorrhoea and menstruation became normal; before operation the menstrual flow had been extremely scanty. There are thus indications other than sterility for active surgical intervention for synechiae.

SUMMARY

A report is given of 11 cases with intra-uterine synechiae. The signs and symptoms and hysterographic appearances are described and discussed. The significance of previous trauma is stressed.

ZUSAMMENFASSUNG

Die Verfasser berichten über 11 Fälle mit intrauterinen Synechien. Das hysterographische Aussehen und die klinischen Symtome derselben werden diskutiert.

RÉSUMÉ

Présentation de 11 cas de synéchies intra-utérines et description de leurs aspects hystérographiques et des symptômes cliniques.

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ECCENTRIC CONTRACTIONS OF THE GALLBLADDER IN CHOLECYSTOGRAPHY

by

Lars Andrén and *Georg Theander*

The filled gallbladder in cholecystography and cholegraphy usually appears as a smoothly rounded, oval, or pear-shaped organ, and its response to cholecystokinetic media is a concentric contraction without appreciable change in shape. Cholecystography sometimes, however, reveals a gallbladder deformed by variable and irregular contractions. This phenomenon appears to have received no attention in the literature.

Eccentric contractions, when marked, may result in local narrowing of the gallbladder so that it becomes tortuous or lobate in shape (Fig. 1). Large circumscribed indentations may appear, resembling those produced by tumour masses in or outside the wall of the gallbladder (Fig. 2, a to c), and the part of the viscus situated above or below the area of contraction may bulge like a balloon (Fig. 2d). A longitudinal or spiral folding may occur, and the gallbladder may appear to be twisted about its long axis (Figs. 2e and 3). The eccentric contractions sometimes produce only shallow indentations or flattening of parts of the gallbladder wall.

The dynamic nature of the phenomenon is apparent on fluoroscopy or serial roentgenography. The shape of the gallbladder is then seen to change

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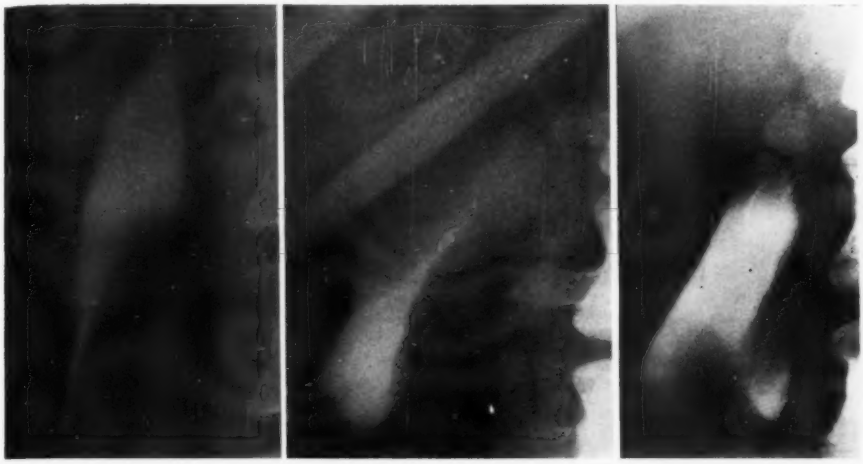
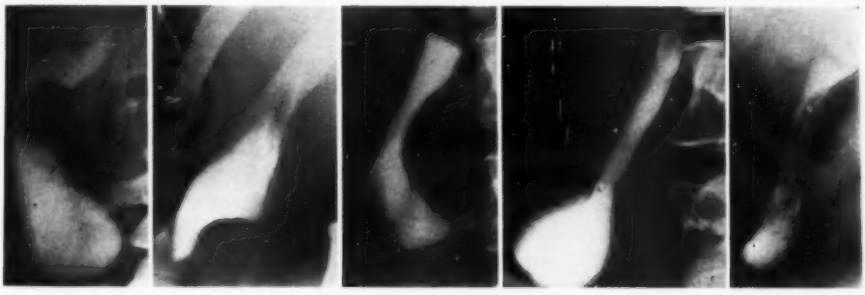


a b c

Fig. 1. a) Local narrowing, b) tortuousity, and c) pseudo-lobation of gallbladder, all produced by eccentric contractions.



a b c d e

Fig. 2. a) to e) Marked deformation of gallbladders caused by eccentric contractions. d) Balloon-like bulging of part of gallbladder. e) Longitudinal folding.

spontaneously, on change in posture, or on the application of pressure to the region (Figs. 4 and 5). Thus, pressure applied to a bulging part of the gallbladder may cause contractions to that part, with simultaneous bulging of areas previously contracted. The movements of the wall of the gallbladder are sometimes so rapid that it is difficult to obtain a properly defined roentgenogram of the organ.

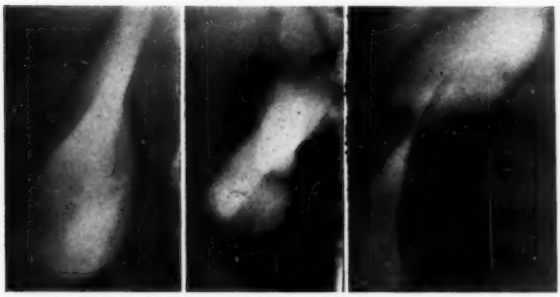
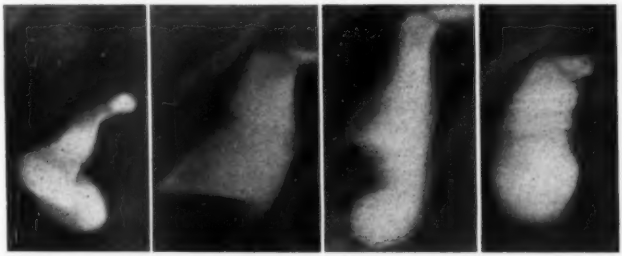


Fig. 3. Spiral folding and twisting of gallbladders.

When eccentric contractions are present the gallbladder is smaller than when it has been filled by the same or some other contrast medium which has not produced contractions (Figs. 5 and 6). This reduction in size is often striking (Figs. 2b, 2e, and 5). The bile ducts are rarely shown in the presence of eccentric contractions but a fatty meal may be followed by further reduction in the size of the gallbladder, and expulsion of contrast medium into the bile ducts (Fig. 6, c to d); the eccentric contractions may then disappear.

Of the routine cholecystographic and cholegraphic contrast media (Bilitrast, Biligrafin, Biligrafin Forte, Telepaque, and Bilijodon-Natrium), used over long periods in our department, eccentric contractions of the gallbladder occurred only after the use of those contrast media containing iopanoic acid (Telepaque) and its sodium salt (Bilijodon-Natrium) (both referred to as iopanoic acid). These contrast media were employed in a dose of 3 g and if this failed satisfactorily to demonstrate the gallbladder on the following day, an additional dose of 3 g was given. When eccentric contractions occurred they usually did so after a single dose; only twice did they appear in cases which had required the repeat dose for satisfactory demonstration of the gallbladder. The phenomenon was on the whole observed almost exclusively in well-filled gallbladders. Upon re-examination with iopanoic acid of cases in which eccentric contractions of the gallbladder had previously been seen, the condition usually reappeared (Fig. 4). But when re-examination was performed with Bilitrast, Biligrafin, or Biligrafin Forte, no such contractions were observed (Figs. 5, e to f and 6, a to b).

The incidence of eccentric contractions cannot be determined with the same accuracy in all groups of cases in a clinical material of cholecystographic examinations. Insufficient filling of the gallbladder or the presence of large or numerous gallstones may make it difficult or impossible to



a b c d

Fig. 4. Recurrence and variability of eccentric contractions: a) January 1957, b) to d) August 1957.

demonstrate the phenomenon. The following analysis was therefore based on well-filled gallbladders without calculi. In the vast majority of these cases it was easy to decide whether eccentric contractions occurred or not; in doubtful cases the phenomenon was regarded as being absent.

Of 2,443 patients examined with iopanoic acid (the sodium salt) in our department in 1957, demonstration of the gallbladder was satisfactory in 1,351. The incidence of eccentric contractions of the gallbladder in this material is given in the table below and in the Diagram. There was a highly significant over-representation of the condition in women (see the table) and then in the 30 to 49 year age group (Diagram); no significant difference was found with age in men.

Table

Sex incidence of eccentric contractions of gallbladders containing no stones and filled by the sodium salt of iopanoic acid

	Numbers of patients	Eccentric contractions	%
Men	536	12	2
Women	815	90	11
Total	1,351	102	8

Discussion

The occurrence of eccentric contractions of the gallbladder in cholecystography with iopanoic acid but not with Bilitrast, or in cholegraphy with Biligrafin or Biligrafin Forte, suggests that these contractions are produced by the contrast medium. This assumption is supported by the observation that the phenomenon occurred almost exclusively in well-filled gallbladders, *i. e.* in gallbladders containing contrast medium

in high concentration. As a matter of fact, in common with other cholecystographic media for oral administration, iopanoic acid if taken uncoated causes an intense sensation of burning in the mouth, pharynx, and oesophagus, which may persist for hours. Even after absorption and excretion the substance seems to retain its irritating properties, as indicated by the occasional symptoms of pain on micturition. It sounds reasonable to assume that eccentric contractions of the gallbladder might be due to local irritation of the wall by the contrast medium.

The eccentric contractions were accompanied by a diminution in the size of the gallbladder like the concentric contraction produced by the administration of cholecystokinin or a fatty meal. Nevertheless the bile ducts were rarely seen in examinations in which eccentric contractions occurred. This is all the more remarkable since the concentration of contrast medium in the gallbladder was usually high, and iopanoic acid is known to show the bile ducts in a high percentage of cases. The eccentric contractions might be the result of an incoordinated action of the musculature without effective expulsion of the contents of the gallbladder. The action of a fatty meal, however, can provoke partial evacuation of the gallbladder just as when eccentric contractions are not present. Thus, any such incoordination of the muscular activity does not seem to interfere with the normal response to cholecystokinin.

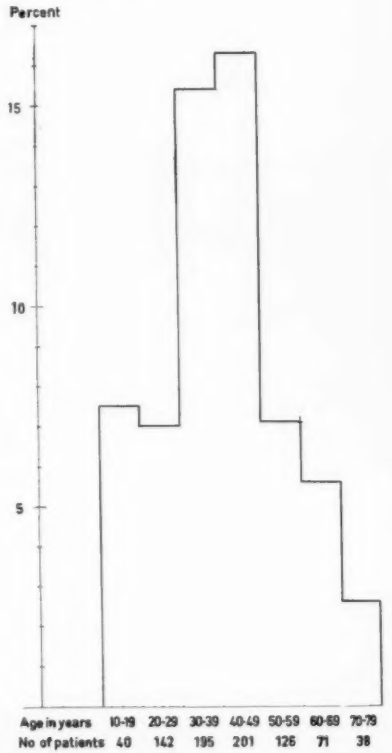
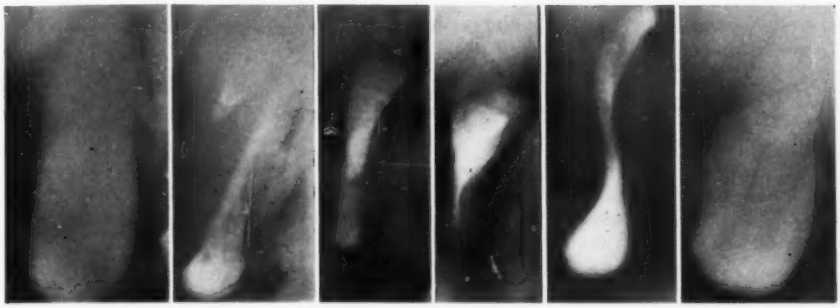


Diagram. Age distribution in women of eccentric contractions of gallbladders containing no stones and filled by the sodium salt of iopanoic acid.

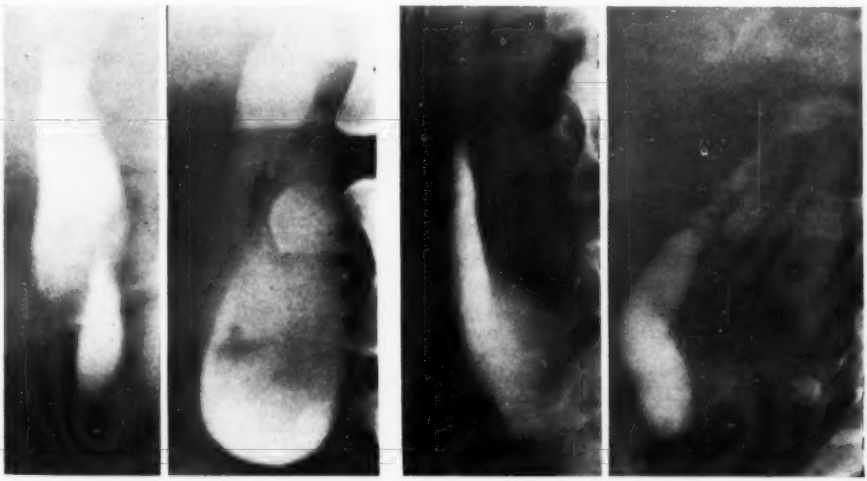
Cholecystitis and cholelithiasis are, as known, more common in women than men. In the present material a significant sex difference was found in the incidence of eccentric contractions of the gallbladder. If this phenomenon, as suggested above, is caused by the local action of the cholecystographic medium, its difference in frequency with sex might possibly be due to some difference in the sensibility or motility of the gallbladder, which might in turn be related to the sex difference in gallbladder disease.

An interrelationship between the susceptibility to eccentric contractions and the liability to gallbladder disease might also be responsible for the overrepresentation of eccentric contractions of the gallbladder in women between the ages of 30 and 50.



a b c d e f

Fig. 5. Gallbladder filled by iopanoic acid: a) without (June 1956), and b) to d) with eccentric contractions (October 1956). e) Gallbladder filled by iopanoic acid and f) by Bilitrast.



a b c d

Fig. 6. Gallbladder filled by: a) iopanoic acid, b) Biligrafin Forte. c) Eccentric contractions. d) After fatty meal.

SUMMARY

Eccentric variable contractions of the gallbladder were observed in 8 % of 1,351 cholecystographies in which filling was obtained with iopanoic acid. They were more common in women than in men, and then particularly in ages between 30 and 50 years. The relationship between the age and sex distribution of the phenomenon and gallbladder disease is discussed.

ZUSAMMENFASSUNG

Exzentrische variable Kontraktionen der Gallenblase wurden bei Cholecystographien mit Iopansäure beobachtet. Sie traten bedeutend häufiger bei Frauen, speziell im Alter von 30 bis 50 Jahren, auf. Die Relation zwischen der Alters- und Geschlechtsverteilung dieses Phänomenes und der Gallenblasenkrankheit wird besprochen.

RÉSUMÉ

Les auteurs ont observé des contractions excentriques variables de la vésicule biliaire au cours de la cholécystographie par l'acide iopanoïque. Ces contractions sont beaucoup plus fréquentes chez les femmes, en particulier entre 30 et 50 ans. Les auteurs examinent le rapport entre la distribution en fonction de l'âge et du sexe de ce phénomène et celle des affections vésiculaires.

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PHYSICAL MEASUREMENTS ON THE LONDON HOSPITAL PICKER C 3000 COBALT UNIT

by

L. A. W. Kemp and *J. E. Burns*

A Picker C 3000 Cobalt Unit was installed in The London Hospital in April 1956. In general form it resembles quite closely a conventional deep therapy roentgen unit. The head may be angulated about the usual two axes at right angles to one another, while the whole head plus yoke may be raised and lowered from the pedestal. Motorised lateral movement of the whole pedestal is also possible.

The source is mounted at one end of a heavy alloy bar which is situated along a diameter of a lead-filled 'shutter' wheel. Rotation of the wheel through 180° interposes the heavy alloy bar between the source and the exit port, and brings the source more or less to the centre of the head. Total rotation time of the shutter wheel is 5 to 6 seconds, but the effective opening and closing time with a 2 cm diameter source is less than half a second.

The unit is fitted with the extremely efficient and elegant Johns-MacKay collimator (JOHNS and MACKAY 1954) which provides, at 80 cm S.S.D., continuously variable square or rectangular field sizes from 4×4 cm to 20×20 cm. The collimator incorporates an optical beam simulator, and also a distance-localising arrangement in which the images of two lamp filaments meet on the skin when the latter is at the correct S.S.D.

The source, supplied by Oak Ridge, had an initial activity of approximately 1,500 curies.

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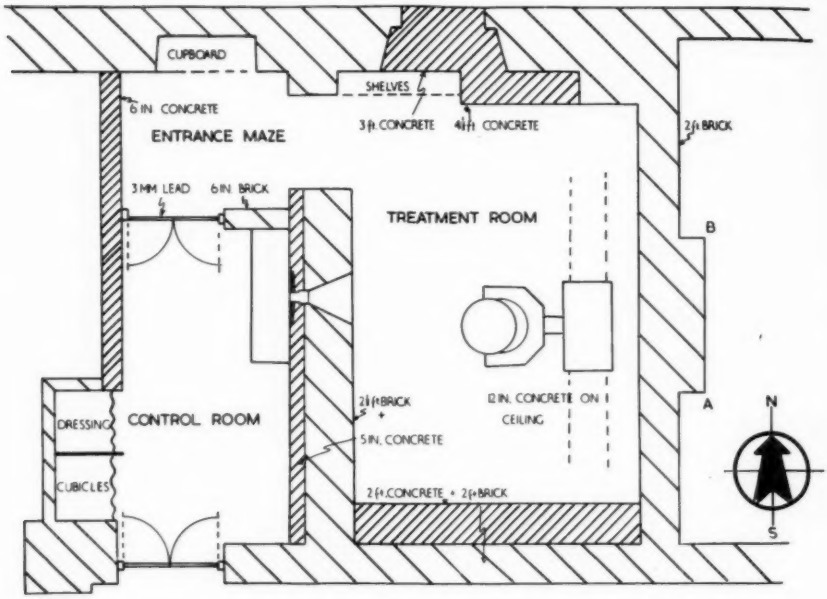

Fig. 1. Plan of The London Hospital cobalt room.

Protection

A plan of the room layout is shown in Fig. 1. The site comprised a basement room in the original part of the hospital building, approaching 200 years old, with brick walls which were, in places, already 2 feet (61 cm) thick. The quality of this brickwork was not known, and the existence of pockets of rubble, or even cavities, could not entirely be ruled out. Substantial amounts of concrete were therefore added, particularly to the south wall (lateral to the unit) which could be irradiated by the direct beam. In addition, the area above the room was one of occasional occupancy, and concrete of about 30 cm thickness had to be added below the original ceiling. This was achieved by a special technique, metal grids being placed below the ceiling for reinforcement purposes and the concrete blown into position, layer by layer, by compressed air.

The calculation of the necessary amounts of concrete to be added were, in the main, based on the data of DIXON, GARRETT and MORRISON (1952) and the stray radiation measurements which were carried out had the purpose, not merely of ensuring that the protection provided was in fact adequate, but also of enabling as accurate a confirmation as possible to be

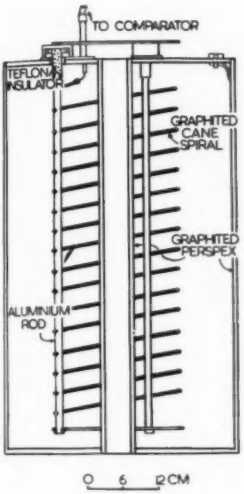

Fig. 2 (to the left). Sectional drawing of the large protection chamber specially constructed for the accurate survey of stray radiation. The instrument is perspex-walled and has a graphited cane collecting spiral. This chamber has applications in the ionometric assay of gamma-emitting radioisotopes.

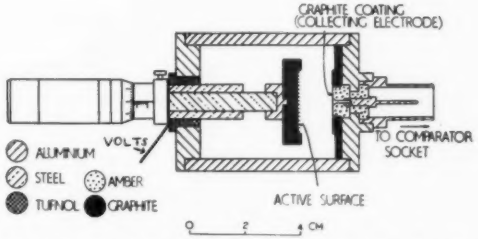

Fig. 3. Sectional drawing of the beta-ray monitor chamber providing a standard reference current. Opposite the collecting electrode is a graphite plaque coated with S^{35} (or Pm^{147}). Adjustment of the intervening gap provides ready control of the current. This chamber was used throughout the measurements with the Kemp-comparator. Details to be published elsewhere.

obtained of the original calculations and, therefore, of the data on which they were based.

The two main difficulties involved in such measurements, if they are to be reasonably accurate, are (a) the low level of the dose rates to be observed, and (b) the uncertainty associated with the quality of the multiple-scattered radiation. For the latter reason, a counter system was not employed. Instead, two entirely distinct measuring equipments were used, both based on ionization, with the one serving as some cross-check of the other.

The main equipment consisted essentially of a large cylindrical perspex-walled chamber, details of which are to be published elsewhere. It is shown in section in Fig. 2. This was cable-coupled to a Kemp-comparator (KEMP 1946, 1954; KEMP and BANFIELD 1957) which enabled the ionization current from the chamber to be measured directly as a percentage of a standard reference current derived from a beta-ray 'monitor' chamber (Fig. 3) plugged into the other side of the comparator. The equipment was calibrated by means of radium sources, and subsequently standardised sources of I^{131} and Au^{198} were employed to confirm that the chamber had no significant quality dependence, at least over the quality range from radium gamma rays down to Au^{198} gamma rays. The equipment was calibrated to provide three ranges, corresponding to 100 mr/hr, 10 mr/hr, and 1 mr/hr full-scale. Thus dose rates of the order of 0.1 mr/hr could be

measured accurately, since the scale of the comparator consisted of 100 equal divisions spread over 180° of the dial.

Except over the lower range of dose rates, readings were also taken with an Ekco pistol-type gamma ray monitor Type 1118A. This instrument agreed well with the large chamber readings, except where multiple-scattered radiation was involved (e. g. in the room maze), where discrepancies occurred. On the whole, however, the agreement between the two, quite different, measurement techniques was gratifying.

Check of original protection calculations. The only walls that can receive the direct radiation from the unit are on the north and south sides of the room. Measurements on the outside face of these walls, using a 20 × 20 cm direct beam with the source 4 metres from the outside of the wall, show excellent agreement with the data of DIXON, GARRETT and MORRISON, namely within one half-value layer in fifteen or so. The dose rate was found to be nowhere greater than 2.5 mr/hr.

The east wall behind the unit was not made so thick, as the beam cannot point towards this wall. Agreement with the calculations was again good, the dose rate being nowhere greater than 0.42 mr/hr, even with the worst possible set-up.

A stop was attached to the yoke of the head to prevent angulations of greater than 45° towards the west (control) wall. With this angulation the direct beam strikes the floor of the treatment room at the foot of the wall, but cannot strike the wall itself. A body-phantom was set up to simulate the worst possible conditions which could obtain with respect to this wall. The dose rate at the position of the radiographer's feet was then found to be 1.6 mr/hr, and in the position occupied by the radiographer's chair, 0.45 mr/hr. These dose rates, whilst quite satisfactory (1/5th to 1/14th M. P. D.), are higher than the calculated value by a factor of 2 or 3, and since the bulk of this wall is composed of the original brickwork there is the possibility that the absorption of this particular brickwork did not in fact come up to expectations.

The main purpose of the measurements in the maze was to provide some idea of the level of radiation which would be experienced by anyone entering the maze when treatment was in progress and before the shutter wheel had moved appreciably to effect a closure. A phantom was set up in the most unfavourable position, and measurements made at the points indicated in Fig. 4. The results were: Point A, 21.5 mr/hr; Point B, 31 mr/hr; Point C, 92 mr/hr; Point D, 104 mr/hr; Point E, 116 mr/hr; Point F, 37 mr/hr; Point G, doors open, 7.4 mr/hr; Point G, doors closed, 0.3 mr/hr. It is seen that the level of radiation in the maze, even in the worst possible conditions, is far from serious (about 10 to 20 times M. P. D.). The dose rate 1 foot outside the maze doors is only slightly above M. P. D., even with the doors open.

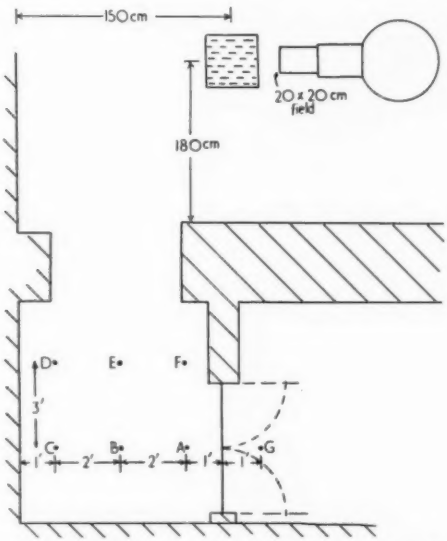

Fig. 4. Phantom set-up for the investigation of conditions inside the room maze.

For measurements on the protection afforded by the ceiling two distinct phantom set-ups were used: (a) the head of the unit was put into 'rotation' and angled over into the extreme position, pointing 30° upwards with a 10×10 cm field (considered to be the largest which would be used for rotation) into an elliptical body phantom, (b) a 20×20 cm field aimed horizontally into the phantom. For both set-ups the maximum dose rate observed in the rooms above was 8.7 mr/hr, only slightly in excess of M. P. D. and quite satisfactory in view of the fact that this space is one of occasional occupancy only.

Average working conditions. Measurements were carried out in the control room and the corridor adjacent to the south wall, using a 20×20 cm field aimed vertically downwards into a large phantom, the unit being centrally positioned in the room. This was considered to represent average working conditions. The dose rates observed outside the room did not anywhere exceed 0.04 mr/hr (about 1/150th of the M. P. D., a very satisfactory result indeed).

Measurements on the head itself. These were carried out (a) by means of the Ekco Pistol Monitor (see above), (b) by a Geiger counter probe (whose readings were calibrated by comparison with those of the pistol monitor at selected points on the head), (c) radiographically, by films.

The results which follow refer to the head pointed vertically downwards, the source being in the off-position. Over the surface of the upper hemisphere of the head the level was about 5 mr/hr, except for a small area in the neighbourhood of the upper side of the shutter mechanism cover, where the general level was about 10 mr/hr. A large film placed over this region revealed that there was a radiation 'leak' over a narrow circular arc approximately 12 cm or so long and 14 cm radius of curvature. The blackening was approximately 1 mm wide only, and corresponded to a dose rate of about 70 mr/hr. It is not considered that this 'leak' represents any significant hazard, especially in view of the fact that this region on the head is normally well out of the way inside the yoke. Over the surface of the lower hemisphere of the head, the dose rate was everywhere below 2.5 mr/hr.

Output of the unit

The primary instrument employed in the measurement of the output was a Victrometer dosemeter (HARLEN 1955), a 4 mm thick perspex build-up cap being added to the chamber to ensure electronic equilibrium at gamma ray qualities. (The instrument had been recently calibrated at the National Physical Laboratory using a Van de Graaff machine and a graphite chamber as a reference standard.) The output of the unit was measured with the chamber free-in-air at 80 cm from the source, using a 4×4 cm field to avoid irradiating an appreciable length of the stem of the chamber. On 7th May 1956 the output thus obtained was 45.6 r/min.

Overall field factors

'Build-up' studies (see below) indicated that the maximum dose rate (corresponding to the '100' level in central axis depth dose studies) occurs at approximately 5 mm below the surface of a unit density phantom. A variety of methods may be employed to derive the dose rate at this '100' level (for any given field size) from the basic output of the unit measured free-in-air at 80 cm (as just described) with one particular field size (4×4 cm in our case, see above).

We chose to combine into a single 'overall field factor' the five relevant individual factors. These are as follows:

1. The factor accounting for the variation with field area of the output free-in-air at 80 cm from the source, which ranged up to 1.07 for a 20×20 cm field. This was studied by means of a small thimble chamber (known to be free of stem leakage effects due to radiation) cable-coupled to the comparator, into the other side of which was plugged the beta ray monitor (see Fig. 3).

2. The backscatter factor, which, for each field size, was measured by comparing the output free-in-air at 80 cm with the corresponding dose rate when a unit density phantom had been added in such a way as to provide 'half-immersion' conditions for the chamber. Backscatter factors so derived are depicted graphically in Diagram 1, and are in good general agreement with those published by other workers.

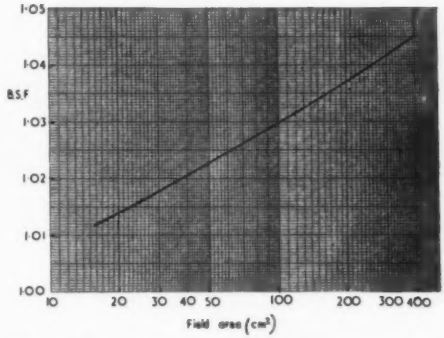

Diagram 1. Variation of backscatter factor with field area.

3. An inverse square law factor to convert the dose rate at 80 cm to that obtaining at 80.5 cm (the distance of the '100' level from the source).

4. An absorption factor appropriate to the 5 mm of unit density material thus interposed. This absorption correction was derived, for each field area, from the slope of the linear portion of the corresponding 'build-up' curve beyond the maximum, since this yields an absorption factor measured with the appropriate geometry, *i. e.* scatter being allowed to play its full part in reducing the apparent absorption of the interposed 5 mm layer.

5. The factor converting roentgens to rads. For soft tissue this was taken as 0.975 (based on a value of W of 34 ergs per ion pair).

For a given area, all five factors multiplied together give the 'overall field factor' converting the output in roentgens per minute at 80 cm from the source 'free-in-air' with a 4×4 cm field, to absorbed dose rate in rads per minute at the '100' level of the given field. It was possible in later experiments to obtain a precise confirmation of the relative variation of overall field factor with field area by an independent method.

The overall field factors, as a function of field area, are shown in Diagram 2. This information is, strictly speaking, for square fields, but the inset curve in the diagram shows that the correction for elongated fields is less than 1% even for the maximum elongation (5 : 1) possible with the Johns-Mackay collimator.

Build-up studies

For 'build-up' (and percentage depth dose) measurements a special flat chamber was constructed with a very thin top (Fig. 5a). The collecting volume of the chamber was 1 mm deep and the collecting electrode 2 cm

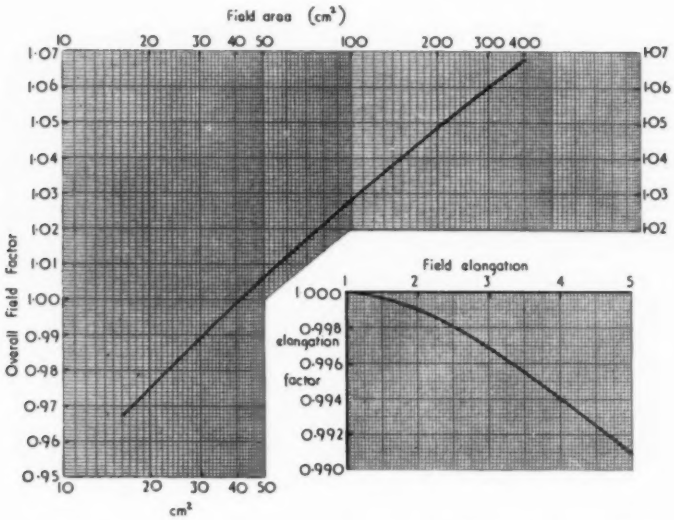

Diagram 2. Variation of 'overall field factor' with field area (square fields): the inset graph shows the correction that must be applied for an elongated field. The overall field factor converts roentgens/min free-in-air at 80 cm from the source with a 4×4 cm field, to the dose rate in rads/min at the '100' level for the required field area.

in diameter. The shapes of the isodose curves even for the smallest field were sufficiently flat in the neighbourhood of the central axis to ensure that there was no significant change in dose rate over the collecting volume of this chamber. The collecting volume was surrounded by an annular air space 1 cm wide, which was, however, filled by a flat perspex annulus for central axis depth dose work (see below). The top covering of the chamber consisted only of graphite cellophane approximately 0.001 in thick, which constituted the voltage electrode of the chamber.

Theoretically the dose rate in the superficial layer of tissue is very small indeed. If this dose rate is determined it gives an indication of the electron contamination of the beam. According to JOHNS (JOHNS and MACKAY 1954), a great deal of electron contamination comes from the source container and the collimating tunnel just in front of it, and much of it may be removed by inserting in the beam a thin sheet of aluminium just beyond this point. JOHNS also found that a distance of 15 to 20 cm was necessary to minimize electron contamination from the collimator. The Picker unit incorporates both these recommendations; a filter is incorporated in the collimating tunnel, and there is 17 cm from the end of the collimator to the patient's skin.

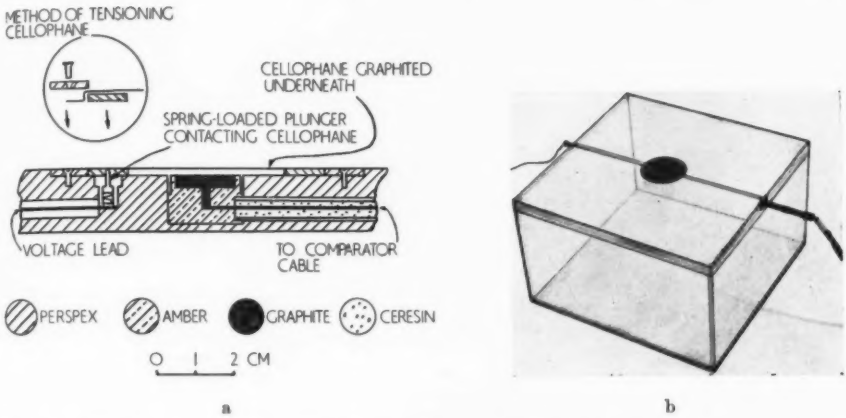

Fig. 5. a) Sectional drawing of electrode system of special flat chamber built into a perspex sheet. The graphite collecting electrode is 2 cm in diameter and the air volume 1 mm thick. b) General view of the chamber in position on backscattering phantom.

For the build-up measurements, the flat chamber was placed on top of a perspex box completely filled with water to provide full backscatter, as shown in Fig. 5b. Thin sheets of perspex were placed on top of the chamber to simulate increasing depths in tissue. The measurements were converted into depth doses in tissue by applying an appropriate I. S. L. correction for increasing depth, together with a correction for the difference in density between perspex and water.

Build-up measurements were carried out for several fields, and those for five square fields are shown in Diagram 3. It is seen that, as expected, the electron contamination increases steadily with field size, causing the skin dose to rise from 18% of the maximum in the case of the 4×4 cm field, to just over 50% for the 20×20 cm field. These figures are very satisfactory, and compare favourably with other published data.

Build-up curves were also measured with and without compression cones added to the collimator. These compression cones are made of perspex, being open-ended and slightly larger than the radiation field to minimize irradiation of the perspex with consequent increase in electron contamination. The increase in skin dose on the central axis varied from 30% for the 4×6 cm cone to 13% for the 10×15 cm cone. This effect, though significant, is not serious.

Central axis percentage depth doses for square fields. As already stated, Diagram 3 does, in effect, show the first part of the percentage depth dose curves from the surface to 5 mm depth for square fields ranging from 4×4 to 20×20 cm.

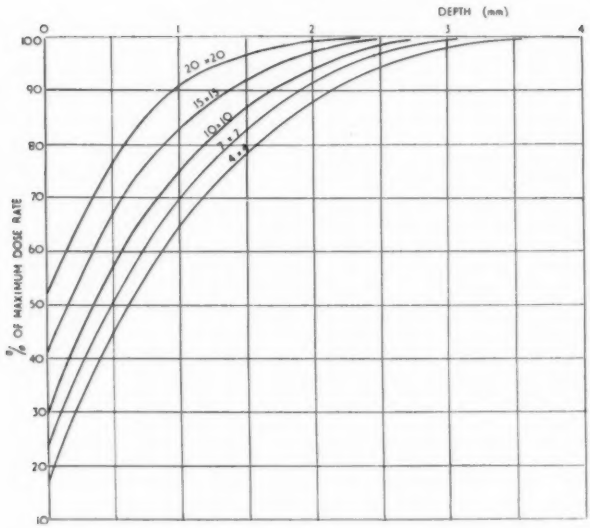

Diagram 3. Variation of central axis percentage depth doses ('build-up curves') in the superficial layers for 4×4 cm, 7×7 cm, 10×10 cm, 15×15 cm and 20×20 cm fields.

For measurements of percentage depth dose at greater depths than 5 mm the experimental set-up was as shown in Fig. 6. A number of runs with different field areas were carried out. These were combined with further measurements on the variation with area of the dose rate (and hence the percentage depth dose) at a number of depths in the phantom. The smoothed results are shown in Diagram 4. Measured percentage depth doses for particular fields are evenly distributed about these average curves.

Measurements were carried out on the absorption of the beam in water to enable percentage depth doses for 'zero field area' to be calculated. A small chamber was placed 175 cm from the source using a 2.5 cm diameter beam directed vertically downwards. A perspex cylinder, inside which various depths of water could be arranged, was placed halfway between the source and chamber. This arrangement provided good geometry in which the amount of scattered radiation reaching the chamber was negligible. The HVL of the radiation in water was found to be 10.8 cm, which is to be compared with the theoretical value of 11.0 cm for Co^{60} radiation (JOHNS et coll. 1952).

The main source of data with which we compared our percentage depth doses is that provided by Professor JOHNS in 'Central axis depth

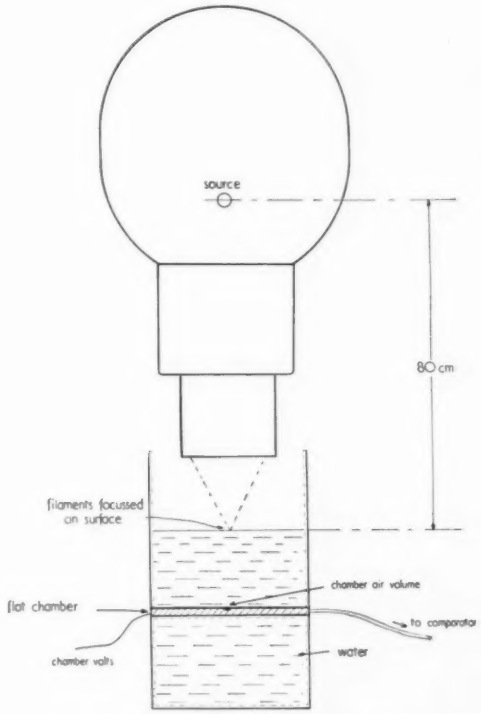

Fig. 6. Experimental set-up for measuring central axis percentage depth doses.

dose data', 1953. The two sets of results never disagree by more than about 3% of the dose at any particular depth, being virtually identical at the largest fields. Our percentage depth doses increase more or less steadily over JOHNS' values as the field area is decreased. The general agreement is gratifying, and such disagreement as exists can possibly be explained by the fact that JOHNS derived his data using solid lead cones and not the slatted collimator which he later designed, and with which the Picker C 3000 unit is fitted.

Percentage depth doses for elongated fields. An extensive series of measurements was made to investigate the effect of field elongation on percentage depth doses. The scope of the measurements ranged from areas of 32 cm² to 400 cm² and elongations up to 5 : 1. The results are summarized in Diagram 5. On comparison with the data obtained at conventional

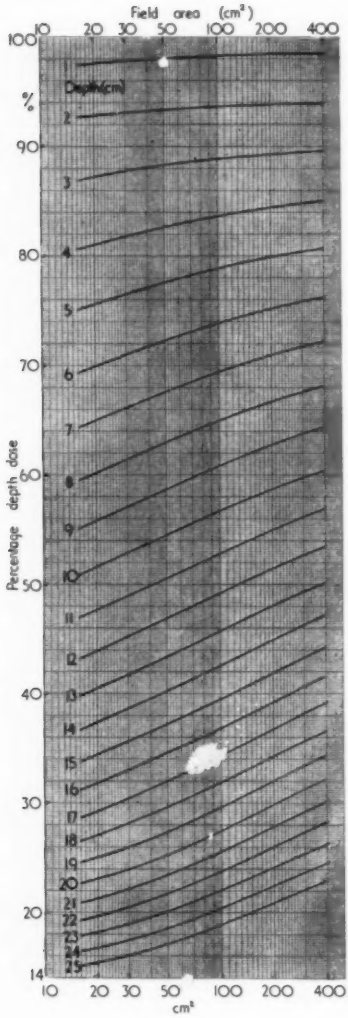

Diagram 4. Variation of central axis percentage depth doses with field area at varying depths, for square fields.

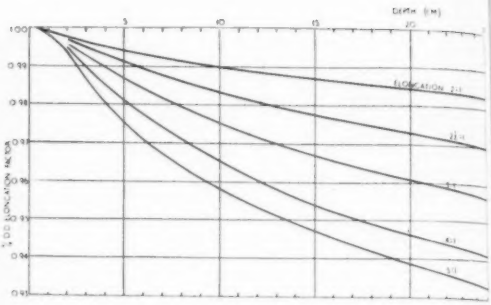

Diagram 5.

Diagram 5. Variation of percentage depth dose elongation factors with depth, for various elongations. These are the factors by which the percentage depth dose for a square field must be multiplied to obtain the percentage depth dose for an elongated field of the same area.

deep therapy qualities analysed by JONES (1949) and DAY (1950), it was found that nowhere was there disagreement by more than 1% of the percentage depth dose for depths down to 20 cm (except for the extreme elongation of 5:1). The accuracy and extent of this agreement was considered to be remarkable.

Isodose curves. The isodose curves were measured using an automatic isodose plotter built by the General Electric Company, Wembley, England, to a design originated by KEMP (1946). The exploring chamber was 6 mm in diameter. No concise method of presenting isodose curves is possible. A fairly complete set of curves for square fields was plotted, together with a few other commonly used elongated fields. It was found that for each axis of a rectangular field (for elongations up to about $2\frac{1}{2}:1$) the shapes of the isodose curves correspond with those of a square field of the same width when due allowance is made for the difference in central axis percentage depth doses.

These isodose curves can be obtained from The Hospital Physicists' Association, Diagrams and Data Scheme, Mount Vernon Hospital, Northwood, Middlesex, England, and are available either as a photostat or printed on translucent paper. The fields available are as follows:

Square fields: 4, 5, 6, 7, 8, 9, 10, 11, 12, 15 and 20 cm square.
Rectangular fields: 20×15 cm, 20×10 cm, 20×5 cm, 15×10 cm, 15×5 cm, 12×8 cm, 10×8 cm, 10×6 cm, 8×6 cm, 7×5 cm, 6×4 cm (both axes of each).

Acknowledgements

We wish to pay tribute to the late Dr. G. BODEN, Director of the London Hospital Radiotherapy Department, whose foresight and initiative were largely responsible for the installation of the Picker C 3000 Unit at The London Hospital, and to acknowledge his interest and encouragement throughout the work described above. Our thanks are also due to Mr. T. A. CLEMENTS for his work on the diagrams.

SUMMARY

Physical measurements on the Picker C 3000 cobalt unit installed at The London Hospital, England, are reported. The strength of the source at installation (May 1956) was approximately 1,500 curies. The measurements include accurate assessment of room protection, backscatter factors, build-up in the superficial layers, leading to the computation of overall field factors relating the standard output in air to the dose rate in rads/min at the '100' level for any given field. Central axis percentage depth doses were in good general agreement with those of JOHNS. Extensive study of the effects of field elongation on depth doses showed excellent agreement with the data of JONES, and of DAY.

ZUSAMMENFASSUNG

Es wird über physikalische Messungen an der Picker C 3000 Kobaltmaschine berichtet, die in »The London Hospital, England« installiert worden ist. Die Quellenintensität betrug bei der Installation (Mai 1956) etwa 1,500 Curie. Die Messungen inkludieren genaue Angaben über den Strahlenschutz des Behandlungsraumes, über Streuungsfaktoren und über den Aufbau der Dosis in den oberflächlichen Schichten, der zur Berechung von allgemein gültigen Feldfaktoren, welche die Standarddosisleistung in Luft zu der Dosisleistung in rad per Minute im 100 %-Niveau für jede Feldgrösse in Beziehung setzt, notwendig ist. Die Tiefendosen im Zentralstrahl standen mit den von JOHNS angegebenen in guter Übereinstimmung. Umfangreiche Untersuchungen der Einwirkung der Feldverlängerung auf die Tiefendosis gaben ausgezeichnete Übereinstimmung mit den von JONES und von DAY angegebenen Daten.

RÉSUMÉ

Présentation des résultats de mesures physiques sur l'appareil de cobalt-thérapie Picker C 3000 installé au London Hospital, Angleterre. La puissance de la source au moment de son installation (mai 1956) était de 1,500 curies environ. Ces mesures comprennent

l'évaluation exacte de la protection du local, les facteurs de diffusion en retour, la répartition dans les couches superficielles, et conduisent à calculer des «facteurs de champ globaux» reliant le débit «standard» dans l'air au taux de dose en rad/min au niveau «100» pour n'importe quel champ donné. Les pourcentages de dose en profondeur sur l'axe central ont été en bonne concordance générale avec ceux de JOHNS. Une large étude des effets de l'élongation du champ sur les doses en profondeur a montré une excellente concordance avec les résultats de JONES et de DAY.

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BOOK REVIEWS

DEMOGRAPHIC STUDIES OF CARCINOMA OF THE UTERINE CERVIX IN SWEDEN. By O. G. A. Berggren. 147 pages, 40 illustrations, 4 maps and 93 tables. Acta radiol. Suppl. 145 (1957). Sw. Kr. 30: —.

With the centralization of the treatment of carcinoma of the uterine cervix to the three Jubilee Clinics of Sweden, in Stockholm (Radiumhemmet), Gothenburg and Lund, and to the Radiologic Clinic in Malmö it has become possible to carry out a comparative investigation of the incidence and severity of the disease and its geographical, occupational and professional distribution. A review of the literature shows that similar studies have been carried out in Denmark, where the existence of a central cancer register for the entire country has produced reliable data on the incidence of cancerous diseases. This system of recording has been in operation since 1942 and it is the first cancer register in the world covering a whole country.

The present material has been collected from the aforementioned four radiologic clinics; it covers the years 1935, 1940, 1945, and 1950, and comprises 1,822 cases. These particular years were selected because complete census data classified according to ages in five-year groups were available. It was moreover possible to obtain information on the occupation, sex, and distribution of the population, for each county in Sweden and for the city of Stockholm. In addition, figures were available for the distribution of the population between towns and rural districts which made it possible to relate the material to these important factors. Carcinoma of the uterine cervix was thus considered in relation to its distribution between towns and rural districts and to the country as a whole. The time factor, *i. e.* the length of the patients' residence in towns or rural districts, could not be considered in this investigation. It would have been practically impossible to collect such data for the entire female population.

A difference in the incidence of carcinoma of the uterine cervix in towns, amounting to approximately twice that in rural districts, has been revealed. This applies to all the four years under survey. The incidence of cases per 10,000 women was 1.97, 1.72, 2.25 and 2.26 for the towns and, respectively, 0.66, 0.81, 0.85 and 1.12 for the rural districts in the four years reported. In counties with a low incidence the proportion of the female population in towns was also low, and where the incidence of the disease was high the proportion of the female population was high. Thus, typical agricultural counties showed a low, and industrial ones a high incidence of cervical cancer. The large cities presented high morbidity figures. In Stockholm, where the incidence was highest, these figures were per 10,000 women 2.19, 2.18, 3.16 and 3.20, respectively, for the four years reported.

In the towns the morbidity showed a decrease from 1935 to 1940, a definite increase from 1940 to 1945, and practically no change from 1945 to 1950. The rural districts had a definite increase in incidence from 1935 to 1940, a slight decrease from 1940 to 1945, although the morbidity was higher than in 1935, and an increase from 1945 to 1950 to the highest incidence in the rural districts. In the country as a whole the morbidity showed a decrease from 1935 to 1940, followed by a significant increase from 1940 to 1945, which was further accentuated from 1945 to 1950. The age group in which cervical cancer occurred most frequently moved towards somewhat younger groups.

During the interval covered by the investigation there was a proportional migration of the female population from the rural districts to the towns. In 1935, about 36 per cent of the female population resided in towns, while the corresponding figure for 1950 was 49 per cent. In 1935 and 1940 a greater percentage of the female population in all age groups lived in rural districts. In 1945 and 1950 the situation had changed so that the majority of the younger age groups had a higher representation in the towns.

The investigation shows that the risk of the development of carcinoma of the uterine cervix is considerably greater for women residing in towns than for those in rural districts. 'Classified milder' forms of carcinoma of the uterine cervix comprised a larger proportion of the cases for each successive year reported in the material studied. This applied for all the radiologic clinics in Sweden. The rural districts showed an almost constant higher percentage of cases of 'classified more severe' forms of carcinoma of the uterine cervix than did the towns. The ages of maximum incidence of carcinoma of the uterine cervix have moved to somewhat younger age groups.

The demonstrated increase in occurrence of carcinoma of the uterine cervix in recent years may be partially but not entirely explained by the migration of the female population from rural districts to towns. The higher incidence in towns must mean that the disease is occurring in increasing numbers of women.

Autoreview.

BONE TUMORS. General aspects and an analysis of 2,276 cases. By David C. Dahlin. 224 pp., 257 figs. Charles C. Thomas, Springfield, Ill., 1957. $11.50.

Primary tumours of bone are rare. The ordinary roentgenologist may see but a few cases in his lifetime and it will be left to individual specialists in large centres to diagnose and treat these conditions.

The author has reviewed more than 2,000 cases in the files of the Mayo Clinic and admirably condensed his experience as well as that of others into one comprehensive volume. The clinical, roentgenologic, and pathologic findings are dealt with in a special chapter for each kind of tumour, the treatment and prognosis also being discussed. A wealth of facts and well-founded opinions are suitably supported by references. There was a 5-year survival rate of 19 % for osteogenic sarcoma in this material, and the author believes that 'these relatively favourable data on a large series of patients should help dispel the unfounded notion held by some that the prognosis of osteogenic sarcoma is so poor that prompt and proper therapy is useless'.

Every roentgenologist, surgeon, and pathologist who seeks information on bone tumours should have access to this excellent volume.

Åke Lindbom.

RADIUM-ISODOSEN. Die Radiumdosierung in 'r'. Von August Verhagen. 103 S., 38 Abb. Georg Thieme Verlag, Stuttgart 1958. DM 19.50.

The volume contains isodose diagrams for a number of radium applicators in general use in Germany. The diagrams are mainly for gynecologic therapy but some are suitable for other purposes such as dermatology and otology; a few are for combinations of two or three different applicators under given geometrical conditions. The explanatory text is in German and English.

The book is of value to those using applicators of these types although in certain instances the accuracy of the diagrams may be questioned. It is noticed, for example, that the values given in Fig. 11 appear to be too high, for in the 2 to 4 cm distance range they exceed those which appear in Fig. 12 for the same applicator with 50 % more radium.

Sven Benner.

RÖNTGENDIAGNOSTIK DES LUMBALEN BANDSCHEIBENRISSES UND SEINER FOLGEN. Von H. H. Weber. Supplementum ad Radiologia Clinica Vol. 26 (1957). 72 S., 36 Abb. S. Karger, Basel 1957. S.Fr. 14.55.

The book deals relatively briefly with the pathology and roentgenologic diagnosis of lumbar disc prolapse based on studies of the literature and personal myelographic investigations of 54 cases of disc prolapse which were verified by operation. The writer contends that retroposition of a vertebra is 'ein auffälliges Frühsymptom des hinteren Bandscheibenrisses mit oder ohne gleichzeitig bestehender Hernie'. He does not state, however, exactly how the retroposition can be measured, nor does he give the minimum retroposition which may be considered pathologic. It would have been better if the book had contained comparative measurements by two investigators on a number of roentgenograms or a comparison by one observer of two different roentgenograms of the same case. The author states that retroposition at the level of the disc in question was present in 75 per cent of his cases and that reduction in the height of the disc was estimated to exist in 50 per cent. No comparative material is reported. The author's view that lumbago and sciatica are absolute indications for roentgenologic investigation is much too dogmatic. The book offers little which is essentially new.

L. Billing.

BOOKS RECEIVED

We acknowledge with thanks under this heading books received for review, which we trust will be regarded as a sufficient mark of appreciation of the courtesy of the sender. The reviews of selected items will appear as soon as opportunity affords.

LA BRONCOGRAFIA. Delle L. Di Guglielmo, L. Pigorini e G. A. Citroni. Il Pensiero Scientifico, Roma 1957.

ANGIOGRAPHIE DER NIEREN. Von E. Vogler und R. Herbst. Georg Thieme, Stuttgart 1957.

ALIMENTARY TRACT OF THE RUMINANT. By David Benzie and A. T. Phillipson. Oliver and Boyd, Edinburgh 1957.

L'ENCÉPHALOGRAPHIE FRACTIONNÉE. Par Giovanni Ruggiero. Masson et Cie., Paris 1957.

ATLAS D'ANATOMIE STÉRÉOTAXIQUE. Par J. Talairach, M. David, P. Tournoux, H. Corredor et T. Koasina. Masson et Cie., Paris 1957.

LES TUMEURS MALIGNES DE L'OREILLE. Librairie Arnette, Paris 1957.

BILATERAL POLYCYSTIC DISEASE OF THE KIDNEYS. By O. Z. Dalgaard. Ejnar Munksgaard, Copenhagen 1957.

ARTERIOGRAFIA ADDOMINALE E DELLE ESTREMITÀ. Delle A. Rabaiotti, L. Rossi e G. Prevedi. Edizioni Minerva Medica, Torino 1957.

DUODÉNUM ET PANCRÉAS. Actualités hépato-gastro-entérologiques de l'Hôtel-Dieu. Sous la direction de Guy Albot et F. Poilleux. Masson et Cie., Paris 1957.

YEAR BOOK OF RADIOLOGY. 1957—1958. Ed. by J. F. Holt, F. J. Hodges, H. W. Jacox and M. M. Kligerman. Year Book Publishers, Chicago 1958.

LA BRONCOGRAFIA NELLA FISIOPATOLOGIA BRONCHIALE. Delle D. Gaudini e G. Juliani. Edizioni Minerva Medica, Torino 1957.

RECUEIL PÉRIODIQUE. Encyclopédie médico-chirurgicale. Radiodiagnostic (Tomes I et II). Editions Techniques, Paris 1957.

THE POSTOPERATIVE CHEST. Radiographic considerations after thoracic surgery. By Hiriam T. Langston, Anton M. Pantone and Myron Melamed. Charles C. Thomas, Springfield, Ill., 1958.

GRUNDRISS DER RÖNTGENTHERAPIE. Von R. Janker und K. Rossmann. Springer Verlag, Berlin 1958.

DER LUNGENBOECK IM RÖNTGENBILD. Von K. Wurm, H. Reindell und L. Heilmeyer. Georg Thieme, Stuttgart 1958.

INFLUENCE DES RAYONS X ET DES RADIATIONS ATOMIQUES SUR LE PATRIMOINE HÉRÉDITAIRE HUMAIN. Par Marie-Odile Réthoré. G. Doin & Cie., Paris 1957.

LA ROENTGENTHÉRAPIE DES AFFECTIONS RHUMATISMALES. Par Pierre Pizon. Masson et Cie, Paris 1958.

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Example:

TILLINGER, K. G.: Papillary cystadenolymphoma. Acta radiol. 28 (1947), 241.

KEITH, A.: Human embryology and morphology. 6th edition, p. 523. Arnold & Co, London 1948.

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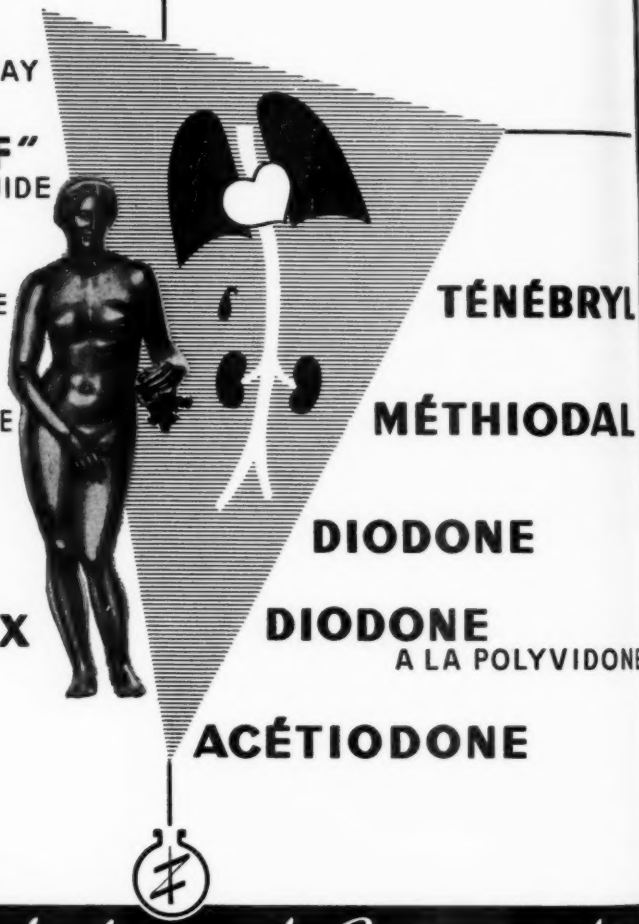

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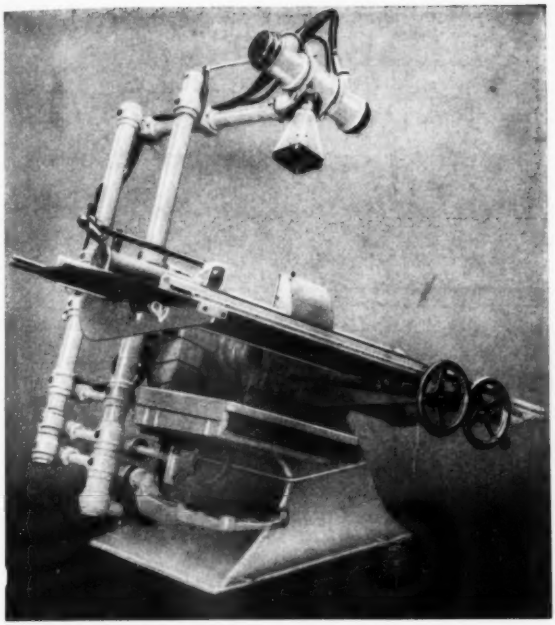

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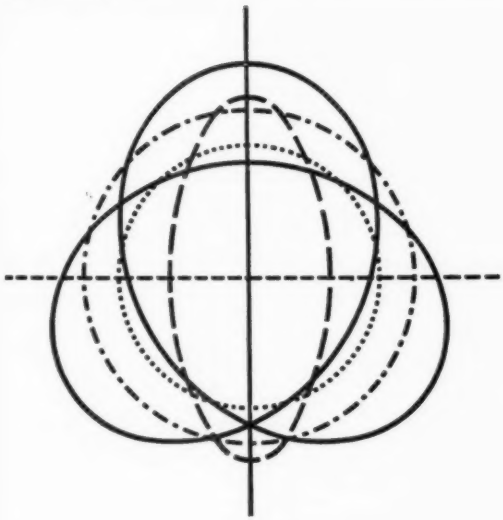

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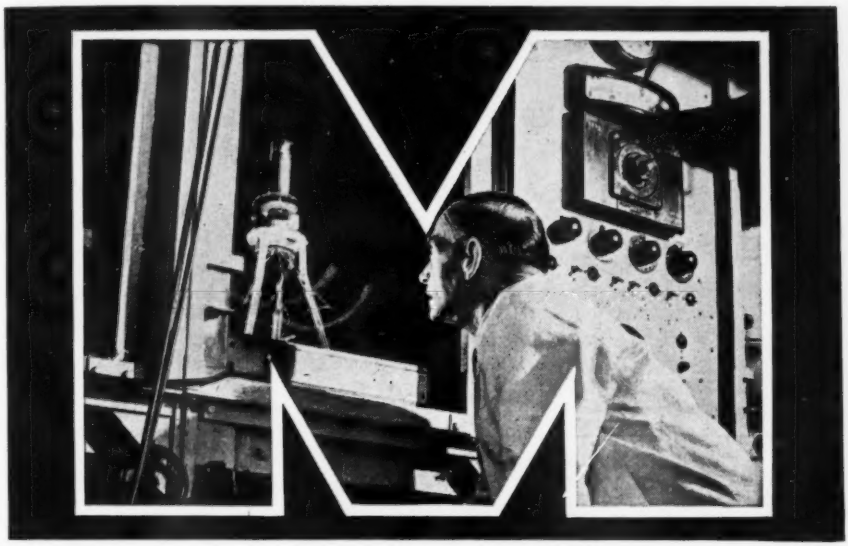

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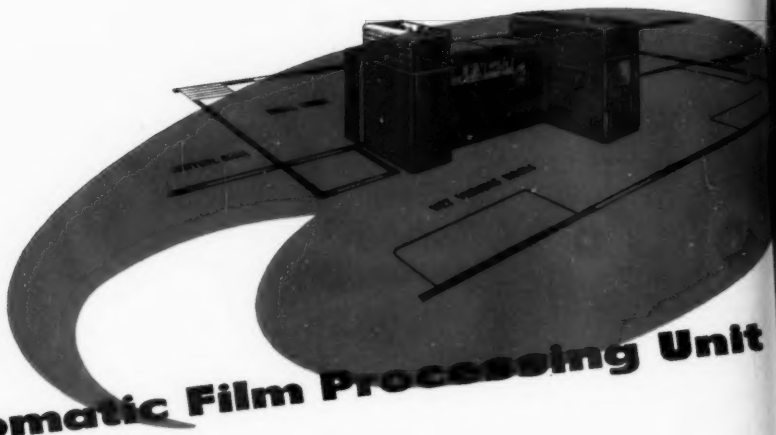

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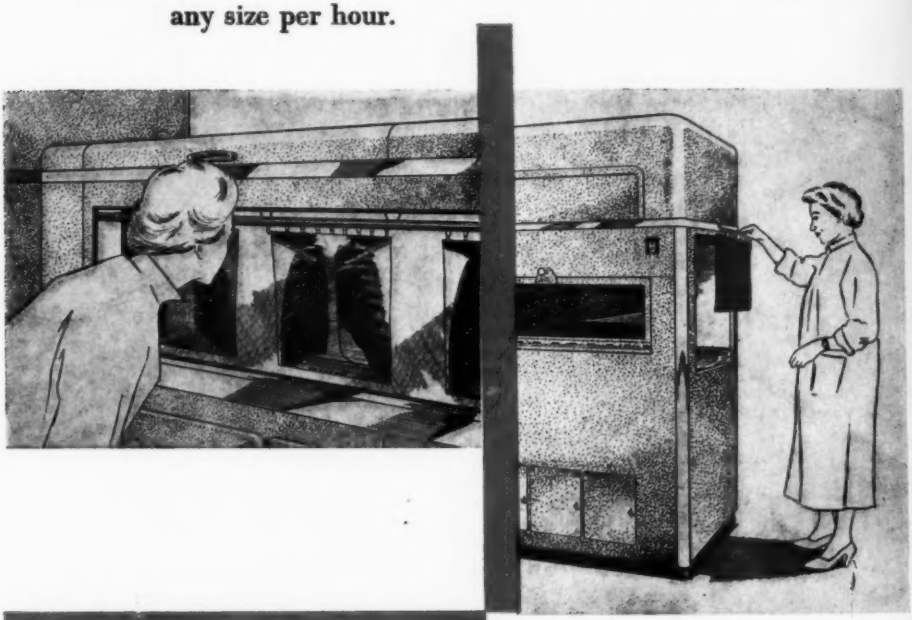
- Automatic film loading.
- Add a cassette conveyor and your dark room is matchless.



ELEMA-SCHÖNANDER

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